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URBAN GREENNESS AND RELATED HEALTH EFFECTS

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URBAN GREENNESS AND RELATED HEALTH EFFECTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Exposure to urban greenness has been linked to a wide range of health outcomes, including many non-communicable health conditions which are presently among the largest contributors to the global burden of disease, such as cardiovascular and metabolic diseases, as well as mental disorders. Half of the world's population now lives in urban areas; often affected by health hazards such as pollutants and heat islands, and characterized by low levels of physical activity, inadequate diets, and decreased access to nature. The overarching aim of this thesis was to investigate associations between residential greenness and different health-related outcomes, including physical activity, adiposity measures and hypertension, as well as general and mental health, both regionally and internationally. In addition, we aimed to evaluate the potentially modifying role of other individual, contextual, and environmental variables, including sociodemographic, behavioral and socioeconomic factors, as well as air pollution, transportation noise and blue space.

We used data from the Stockholm Public Health Cohort ($n=42\,611$), from 2010 and 2014, and the Stockholm Diabetes Prevention Program ($n=5\,126$ and $n=4\,623$, respectively) from 1992–2006, for three of the papers. The fourth paper was a meta-analysis including three cross-sectional surveys from southern Sweden, Spain, and the UK ($N=50\,220$), conducted between 2012 and 2014. We assessed residential greenness exposure using the satellite-derived Normalized Difference Vegetation Index (NDVI) and land-use data. Outcome assessment was based on self-reported data from questionnaires, clinical examinations, and health registers.

Changing residential greenness exposure, because of moving, was inversely associated with walking/cycling. Both moving to a greener and to a less green area were associated with a decrease in exercise. Higher greenness exposure was associated with reduced increase in waist circumference and lower risk of central adiposity in women, but not in men. Exposure to low NDVI levels in combination with high NO_x from road traffic and transportation noise as well as long distance to blue space were associated with increases in waist circumference in both sexes. Increased greenness exposure during 5 years preceding diagnosis was also a predictor of reduced hypertension risk. A more pronounced risk reduction associated with greenness exposure was observed for those exposed to road traffic noise ≥ 53 dB L_{den} or aircraft noise ≥ 45 dB L_{den} , respectively. Green and blue space measures were weakly associated with general and mental health in a meta-analysis of surveys from three countries, and with inconsistent patterns in each of the individual surveys.

In conclusion, our findings illustrate the complexity of the urban greenness-health relationship, and the importance of context and assessing the impact of other environmental exposures. Our results suggest a potentially mitigating role of greenness on negative health effects of environmental exposures, such as air pollution and transportation noise.

LIST OF SCIENTIFIC PAPERS

- I. Persson Å., Möller J., Engström K., Löhmus M., Nooijen C. (2019). Is moving to a greener or less green area followed by changes in physical activity? *Health and Place*, Vol.57, p.165–170.
- II. Persson Å., Pyko A., Lind T., Bellander T., Östenson C.-G., Pershagen G., Eriksson C., Löhmus M. (2018). Urban residential greenness and adiposity: A cohort study in Stockholm County. *Environ. Int.*, Vol.121, p.832–841.
- III. Persson Å., Pyko A., Bellander T., Lind T., Lager A., Östenson C.-G., Pershagen G., Löhmus M., Eriksson C. Long-term exposure to residential greenness and incidence of hypertension. (Under revision)
- IV. Grellier J., Persson Å., Zijlema W., Ambros A., Márquez S., Elliott L. R., Björk J., Triguero-Mas M., Gascon M., van den Bosch M., Nieuwenhuijsen M. J., Löhmus M., Wheeler B., White M. P. A harmonised three-country study of associations between natural spaces in urban environments and self-reported measures of health. (Manuscript)

LIST OF RELATED SCIENTIFIC PAPERS

Persson Å., Eriksson C., Löhmus M. (2018). Inverse associations between neighborhood socioeconomic factors and green structure in urban and suburban municipalities of Stockholm County. *Landsc. Urban Plan.* Vol.179, p.103–106.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
dB	Decibel
ESCA	Health Survey of Catalonia (Enquesta de salut de Catalunya)
GHQ	General Health Questionnaire
GIS	Geographic Information System
GPS	Global Positioning Systems
HPA axis	Hypothalamic–Pituitary–Adrenal axis
ICD-9	International Classification of Diseases, 9 th Revision
ICD-10	International Classification of Diseases, 10 th Revision
IRR	Incidence Rate Ratio
L _{Aeq24h}	Continuous 24 hours A-weighted equivalent sound pressure level
L _{den}	L _{Aeq24h} , with penalties for exposure occurring during evening (5 dB) and night (10 dB)
LMIC	Low and Middle-Income Countries
MAR	Missing At Random
MICE	Multiple Imputation by Chained Equations
NCD	Non-Communicable Disease
NDVI	Natural Difference Vegetation Index
NIR	Near-InfraRed light
NO _x	Nitrogen Oxides
OR	Odds Ratio
RED	Red light
PHS	Public Health in Scania survey (Folkhälsa i Skåne)
PM	Particulate matter
SAMS	Small Area for Market Statistics
SDPP	Stockholm Diabetes Prevention Program
SES	Socio-Economic Status
SPHC	Stockholm Public Health Cohort
TWA	Time-Weighted Average
UA2012	Urban Atlas 2012
UKHLS	United Kingdom Household Longitudinal Survey
WHO	World Health Organization

1 INTRODUCTION

During the last decades, there has been a shift from communicable to non-communicable diseases (NCDs) in the global burden of disease, with NCDs now estimated to account for more than two-thirds of all deaths globally, or 41 million deaths every year (WHO 2018a). During the same period, there has also been a shift in humankind's living environment: from rural to urban, with now more than half of the world's population living in urban areas (WHO & UN-HABITAT 2010). As a result of these changes, NCDs such as cardiovascular and metabolic diseases and their risk factors associated with urban environments are receiving increasing attention. Behavioral factors such as insufficient physical activity and unhealthy diets, and environmental factors such as traffic-related air pollution and transportation noise, are well-known contributors to increased risk of cardiovascular and metabolic diseases (Kempen et al. 2018; Munzel et al. 2017). Until recently, little has been known about health-promoting environmental factors. An increasing body of evidence suggests that one particular environmental factor, often referred to as urban greenness, may have a beneficial role in preventing cardiovascular and metabolic disease (WHO 2016a), and have a range of other positive effects on health and wellbeing (Capaldi et al. 2014; Fong et al. 2018; Kondo et al. 2018; Markevych et al. 2017; Sandifer et al. 2015).

1.1 URBAN RESIDENTIAL GREENNESS

The research area focusing on associations between greenness and health has emerged and grown during the last few decades. No universal term to define green environments has yet been established. Different terms, such as 'greenness', 'green structure', 'green space', 'urban green', 'natural space', 'natural environments', etc., are used to define population exposure to vegetation. The term "urban greenness" may thus include all types of botanical elements in urban landscapes – from flowerbeds to street trees, or refer to specific areas with predominantly natural surfaces (such as *e.g.* parks, forests, and private gardens). In this thesis, *greenness* will be the general term used for any measure of vegetation and other green elements, and *green space* for clearly defined green areas such as parks or forests. For exposure to water bodies such as lakes, the sea, rivers, streams and other "blue environments" or aspects of "blue structure", the term *blue space* will be used. For exposure to greenness as well as blue spaces, the term *natural spaces* will be used.

In the epidemiological literature, two main methods to quantify greenness exposure have been developed, namely cumulative indicators and/or proximity indicators (Ekkel and de Vries 2017). Cumulative indicators estimate the amount of vegetation within a certain area of interest, most commonly circular buffers (generally with 50–2000 m radii) around residential addresses or other locations. When the exact address coordinates are not known, greenness exposure has been estimated in administrative or functional units such as zip code areas.

The type and source of vegetation data vary between studies. Land-use data, available at various national or international agencies or organizations, have been used to calculate proportions of different types of greenness: forest, grassland, parks etc. within the area of

interest. Satellite-derived data, the so-called vegetation indices such as Normalized Difference Vegetation Index (NDVI), Soil-Adjusted Vegetation Index (SAVI) and Enhanced Vegetation Index (EVI) are other frequently used tools to quantify the amount of vegetation within an area of interest. Vegetation indices are calculated based on the land surface reflection and vegetation absorption of light of different wavelengths. The most commonly used vegetation index, NDVI, is calculated by using the formula $NDVI = (NIR - RED) / (NIR + RED)$, where NIR is the reflected near infrared and RED the reflected visible red light. NDVI ranges between -1 and 1, with higher values indicating more photosynthesizing organisms.

Proximity indicators are used to estimate the distance between the study subject's place of residence and a green area of interest (*i.e.* park, forest etc.). The distance may be measured as a Euclidian distance (straight line), or as a network distance (following roads, pathways, etc., *i.e.* the actual accessible route). Occasionally, more qualitative measures are used, such as the biodiversity of a neighborhood (Ekkel and de Vries 2017; WHO 2016a), or perceived qualities, access and availability of greenness (Markevych et al. 2017).

Greenness exposure may also be categorized into availability, accessibility, and visibility indicators (Labib et al. 2020). *Availability* indicators refers to the presence of greenness within a defined area of interest, *e.g.* the number of parks or total park area surrounding subject's locations. *Accessibility* indicators refers to the proximity to defined green areas or locations of interest, either as Euclidean or network distance, or travel time, to parks. *Visibility* indicators refers to the greenness that can be seen from locations of interest, such as views from *e.g.* windows or streets. Visible greenness may be estimated using objective, automated techniques such as image analysis, pattern recognition methods and algorithms, and viewshed analysis (Nguyen et al. 2018; Nutsford et al. 2015; Seiferling et al. 2017).

1.2 GREENNESS AND HEALTH OUTCOMES

According to the World Health Organization, “health” is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO 2020c). This definition implies that “health” and the mission of “health care” should not only include an indication of changes in disease patterns, but also an estimation of human wellbeing and a mission to improve an individual's quality of life. Today, there is an increasing interest in research exploring how neighborhood greenness may affect health-related behaviors and outcomes. The general consensus is that greenness affects human health by promoting physical activity and social contact; decreasing stress; and mitigating air pollution, noise, and heat exposure (James et al. 2015; Rojas-Rueda et al. 2019; Zhang et al. 2020). In addition, higher levels of surrounding greenness are thought to benefit the immune system and metabolism and reduce both cardiovascular disease and premature mortality (Rojas-Rueda et al. 2019). On the other hand, greenness has also been linked to some health risks, such as increased exposure to allergens (*i.e.* pollen, mould spores), pesticides, herbicides, arthropod-borne diseases (*i.e.* Lyme disease, dengue), accidental injuries, and excessive exposure to ultraviolet radiation (Löhmuß and Balbus 2015; Rojas-Rueda et al.

2019). Overall, the epidemiological evidence, however, indicates that exposure to urban greenness is associated with health benefits (Rojas-Rueda et al. 2019).

1.2.1 Physical activity

Physical activity has been defined as “any bodily movement produced by skeletal muscles that require energy expenditure” (WHO 2018b) and involves activities during work as well as leisure time such as carrying out household chores, transportation and exercise. The recommended levels of physical activity for adults aged 18–64 years are ≤ 150 minutes of moderate-intensity aerobic physical activity per week, or ≤ 75 minutes of vigorous-intensity aerobic physical activity per week, or equivalent moderate- and vigorous-intensity activity combined (WHO 2010). Globally, approximately 75% of the population was estimated to meet these recommendation in 2016 with substantial, however, variations between different regions (Guthold et al. 2018). In Sweden, approximately 77% of the population were estimated to meet the recommended physical activity levels. The global trend has been a marginal increase between 2001 and 2016, but with variations between the regions. In high-income western countries, including Sweden, the physical activity level is estimated to have decreased between 2001 and 2016 (Guthold et al. 2018). It should be noted, however, that estimations of physical activity levels are predominantly based on self-reported measures, and investigations of physical activity patterns and levels using accelerometers suggest that levels are substantially lower, with only a few percent of the adult population in high-income Western countries meeting the recommended levels (Troiano et al. 2008; Tucker et al. 2011).

There is a range of well-established, beneficial health effects of physical activity in primary and secondary prevention of major chronic diseases, such as overweight, diabetes, hypertension, different types of cancer, osteoporosis and depression (Penedo and Dahn 2005; Warburton et al. 2006). Physical inactivity, *i.e.* not meeting the recommended physical activity levels, is estimated to be the fourth leading risk factor for global mortality, after high blood pressure, tobacco use and high blood glucose (WHO 2009).

The literature investigating physical activity in relation to greenness exposure includes a review by James et al. (2015), which reported that six of the reviewed nine studies found a moderately positive association between greenness and physical activity. In a more recent review, the same group of researchers (Fong et al. 2018) conclude that the newer studies “further confirm the generally strong link between greenness and physical activity”. However, both reviews were mainly based on cross-sectional studies and there was large heterogeneity concerning the methods of assessing both greenness and physical activity, as well as in the adjustment for confounders. Thus, the authors suggest that future studies need to address these issues to allow for more substantiated conclusions about associations (Fong et al. 2018; James et al. 2015). In a review focusing on leisure services and parks and recreational settings, Kaczynski and Henderson (2007) observed that proximity to parks appears to be associated with increased physical activity in 40% of the studies, but conclude that several of the included studies also reported mixed findings and inverse associations. In addition to greenness, some recent studies have reported that access to blue space may be

important for physical activity. A review by Gascon et al. (2017) presents limited evidence for a positive association between the levels of physical activity and exposure to outdoor blue space, and Pasanen et al. (2019) reported that living nearer the coast is associated with better self-reported general and mental health and that this effect seems to be partially mediated by increased physical activity (primarily walking).

1.2.2 Overweight and obesity

The definition of overweight and obesity is “abnormal or excessive fat accumulation that may impair health” (WHO 2020b), and is based on the index Body Mass Index (BMI). BMI is a measurement of an individual’s weight in relation to height and is calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). The established thresholds for overweight are $\leq 25 \text{ kg/m}^2$ and for obesity $\leq 30 \text{ kg/m}^2$ for adults. However, since BMI mainly reflects energy balance rather than fat distribution and associated cardio-metabolic risks, other measures of adiposity have been developed. Waist circumference (WC) is a measure of central or abdominal obesity, and reflects the accumulation of visceral fat tissue which has been linked to increased cardiovascular disease risk (Ritchie and Connell 2007; Yusuf et al. 2004), and been used in the diagnostic criteria for metabolic syndrome (Grundy et al. 2005). The WHO (2008) has defined central obesity as having a waist circumference of $>80 \text{ cm}$ for women and $>94 \text{ cm}$ for men, a threshold considered to be associated with an *increased risk* of metabolic complications, and $>88 \text{ cm}$ for women and $>102 \text{ cm}$ for men as a threshold associated with a *substantially increased risk* of metabolic complications.

The proportion of the population being overweight or obese is increasing in most countries, with a near tripling of the prevalence in 2016 compared to 1975 (WHO 2020b). In 2016, approximately 39% of the world’s adult population were estimated to be overweight, and 13% to be obese (WHO 2020b). A global trend of increasing prevalence of central obesity has also been observed, with increases of 31% to 48% from the period 1985–1999 to 2010–2014 (Wong et al. 2020).

General overweight and obesity as well as central obesity increase the risk of the major non-communicable diseases and conditions such as hypertension, coronary heart disease, stroke and diabetes, and are also risk factors for osteoarthritis, certain cancers and impaired reproductive functions (WHO 2020b).

The majority of studies investigating the relationship between greenness exposure and adiposity measures have used BMI as their main outcome (Kondo et al. 2018). A systematic review by Lachowycz and Jones (2011) concluded that although the majority of the assessed studies reported a negative or a weak negative association between greenness and overweight/obesity, the evidence of an association was rather limited since many of the studies did not provide sufficient confounding control, were based on self-reported data, and were cross-sectional. Other reviews have confirmed the findings of a weak negative association between greenness and overweight/obesity, but also emphasized the mixed

findings and methodological limitations such as relying on self-reported physical activity and BMI (Fong et al. 2018; James et al. 2015).

A recent systematic review and meta-analysis found that the majority of the included studies reported inverse associations between NDVI and overweight/obesity (Luo et al. 2020). In the meta-analysis, higher NDVI values were associated with lower odds of overweight/obesity, however, other greenness estimates (distance to green space, proportion of green space or number of parks) were not associated with odds of overweight/obesity. The authors concluded that access to greenness might be associated with reduced odds of overweight/obesity, but high between-study heterogeneity and a limited number of studies do not allow for firm conclusions.

1.2.3 Hypertension

Hypertension is a condition characterized by persistently elevated pressure of the circulating blood against the walls of the blood vessels. Blood pressure is assessed based on two readings, the systolic and the diastolic blood pressure. Hypertension is defined as having a systolic blood pressure ≤ 140 mm Hg and/or diastolic blood pressure ≤ 90 mm Hg (WHO 2013). With the increased heart work load and more pressure against the vessel walls, hypertension may increase the risk of myocardial infarction, heart failure, stroke and kidney failure (WHO 2019a). Hypertension is one of the leading preventable risk factors for cardiovascular diseases, and a major contributing risk factor to the global burden of disease and premature death (Gakidou et al. 2017).

The global prevalence of hypertension was estimated to be 20% in women and 24% in men 2015, but with considerable regional differences in prevalence and development (Zhou et al. 2017). Decreasing prevalence has been observed in high-income western countries during the last decades, whereas stable or increasing prevalence has been observed in many low and middle-income countries (LMIC) (Mills et al. 2016). Consequently, LMIC is now where the largest number of hypertensive adults live, 1.04 billion (75%) out of the estimated 1.39 billion worldwide in 2010 (Mills et al. 2020).

The association between greenness and blood pressure has been investigated through epidemiological as well as experimental studies. In experimental studies, the respondents are usually asked to walk in either natural or built environments for a certain period of time. Lower blood pressure in participants visiting a green area has been reported in some (Lanki et al. 2017; Tamosiunas et al. 2014), but not in all of these studies (Hartig et al. 1991). The results from epidemiological studies have been rather mixed. For example, proximity to city parks during the first trimester of pregnancy was associated with maintenance of a normal blood pressure among women residing in Kaunas, Lithuania (Grazuleviciene et al. 2014), and higher levels of greenness were associated with lower systolic and diastolic blood pressure in a cross-sectional analysis of children from two German birth cohorts (Markevysh et al. 2014). In contrast, a twin study investigating the ambulatory (24-h) blood pressure found that residential greenness was inversely associated with night-time systolic blood pressure in

individuals living at the same address their entire life, but among twins who had moved to another address, only early-life residential greenness exposure was significantly associated with night systolic blood pressure (Bijnens et al. 2017). In a cross-sectional study of nearly 25,000 Chinese adults, increased greenness was consistently associated with lower prevalence of hypertension (Yang et al. 2019). No association was observed between residential greenness and blood pressure in a large cross-sectional study of nearly 350,000 participants in the Netherlands (Maas et al. 2009).

1.2.4 General and mental health

While the WHO definition of “health” is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO 2020c), “general health” can, according to the Oxford English Dictionary, be defined as the “the state of health of the body as a whole”. During the last decades, there have been indications of an overall declining trend in reporting less-than-good self-rated health (*i.e.* a trend towards reporting better health) (Hu et al. 2016). However, the self-estimation of general health differs depending on the region, sex, socio-economic status and age. Women appear to report poorer health than men, despite that women have a longer average life expectancy and lower mortality rates at all ages compared to men (WHO 2016b). Low socio-economic status and low education have also been observed to be associated with poor self-reported health (Hu et al. 2016).

According to WHO, mental health is “a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community” (WHO 2020a). Mental health is also closely related to wellbeing and strongly affects the quality of life. Mental disorders include a wide spectrum of problems such as depression, anxiety, bipolar disorder, schizophrenia and other psychoses, developmental disorders (*e.g.* autism) and dementia (WHO 2019b).

Estimates of the global burden of disease (GBD) have found that mental disorders have contributed to more than 14% of age-standardized years lost due to disability (YLDs) during the last 30 years, and have more than 10% prevalence in all 21 GBD regions (James et al. 2018). Mental disorders are recognized as one of the major public health challenges in the WHO European Region, and have been reported to affect about 25% of the population every year (WHO 2015). Mental health disorders are increasing globally, and were found to affect 3 out of 10 adults worldwide during their lifetime in a meta-analysis of 85 surveys across 39 countries (Steel et al. 2014).

To assess the status of general and mental health, a number of different tools have been developed (McHorney 1999). One of the frequently used multi-item tools to assess general health is the Short-Form Health Survey (SF-36), an instrument which assesses general physical and mental health (Ware and Sherbourne 1992). From this, the first item is used as a single question assessing self-rated general health, called Short Form 1 (SF-1). The SF-1 consists of one question only, and is answered by using one of the five provided response alternatives: “In general, would you say your health is: Excellent, Very Good, Good, Fair, or

Poor”. Despite its simplicity, the SF-1 scale has been found to function as a good predictor of an individual’s mortality risk and future health expenditure (DeSalvo et al. 2006; DeSalvo et al. 2009).

The General Health Questionnaire (GHQ-12) was originally developed as a self-administered screening instrument for non-psychotic mental illness in patients, but has later been used as a tool to assess mental health in general population settings (Lundin et al. 2016). According to previous studies, the average GHQ-12 scores may vary between countries and regions, indicating general differences in mental health of different populations (Goldberg et al. 1998; Lundin et al. 2016). The between-population difference of average GHQ-12 scores affect both the optimal threshold value when assigning which individuals are “at risk” for bad mental health and the overall agreement between the GHQ-12 and predicted diagnosis (Goldberg et al. 1998). It is therefore recommended that when the GHQ-12 scores are converted to a binary variable, the threshold levels for “at risk” and “not at risk” should be population-specific and determined according to the mean score of the study population (Goldberg et al. 1998).

The various methodological approaches used in previous research of the associations between green/blue space and indicators of general/mental health and well-being include experimental and observational studies (Gascon et al. 2015; Gascon et al. 2017). Previous experimental studies have explored differences in physiological, cognitive and affective measures in relation to natural environments, in field as well as in laboratory settings (Aspinall et al. 2015; Berman et al. 2012; Hartig et al. 2003; Ulrich et al. 1991). A number of observational studies have investigated associations between green/blue space and general/mental health and well-being using the GHQ12, SF1 and other instruments (Alcock et al. 2015; Dadvand et al. 2016; Mitchell et al. 2015; Van den Berg et al. 2016) as well as salivary cortisol (Roe et al. 2013). Many of these studies report positive associations between green/blue space exposure and mental health/wellbeing (Bratman et al. 2019; Gascon et al. 2015; Gascon et al. 2017; Hartig et al. 2014; Ives et al. 2017; Jarvis et al. 2020; McDougall et al. 2020; Wendelboe-Nelson et al. 2019; White et al. 2017). A review by Wendelboe-Nelson et al. (2019) indicated that the differences between study designs, definitions, outcomes and the way of reporting in previous studies, made it difficult to aggregate the evidence. Similarly, a review by Nuñez-Gonzalez et al. (2020), concluded that there was insufficient evidence to make any firm conclusions on the effects of built environment interventions on mental health outcomes as the collected evidence was characterized by high heterogeneity concerning the outcomes and measures, and included many low-quality studies.

1.3 MECHANISMS INVOLVED IN THE GREENNESS-HEALTH RELATIONSHIP

The underlying psychophysiological mechanisms of the greenness-health relationship are currently not fully understood. The World Health Organization (2016a) suggests nine possible pathways: improved relaxation and restoration, improved social capital, improved functioning of the immune system, enhanced physical activity together with improved fitness and reduced obesity, anthropogenic noise buffering and production of natural sounds,

reduced exposure to air pollution, reduction of the urban heat island effect, enhanced pro-environmental behavior and optimized exposure to sunlight and improved sleep. Below we present three main pathways that have been the focus for this thesis. Greenness may:

- Provide inviting settings for physical activity, for recreational (*e.g.* walking and cycling) as well as routine purposes such as active transportation; a destination as well as a route (Fong et al. 2018; Kaczynski and Henderson 2007).
- Enable improved and facilitated relaxation, restoration and stress recovery (Hartig et al. 2014; Kondo et al. 2018; Markevych et al. 2017). This suggested psychophysiological link has been supported by a number of experimental and observational studies which have found associations between greenness and stress-related biomarkers and self-reported perceived stress, suggesting a stress-buffering effect of greenness (Bratman et al. 2015; Park et al. 2010; Ward Thompson et al. 2012; WHO 2016a).
- Mitigate harmful effects of exposure to environmental stressors such as air pollution, noise and heat (WHO 2016a). A growing body of evidence has linked anthropogenic noise from road, railway and aircraft transportation to a range of health outcomes, including an increased risk of cardiovascular and metabolic diseases (Kempen et al. 2018). Greenness has been suggested to mitigate the effects of noise exposure either via acoustic noise-buffering or noise-masking by natural sounds or via a psychological influence, reducing the harmful effects of noise (WHO 2016a). Furthermore, there is evidence of associations between air pollution and cardiovascular as well as metabolic diseases (Bourdrel et al. 2017; Munzel et al. 2017). The exposure to pollutants from traffic, energy production facilities and other sources may be mitigated by the presence of plants, trees and natural surfaces (*e.g.* moss and grass); by acting as barriers, and by removal of particles through dry deposition to plant surfaces and gaseous air pollution by uptake via leaf stomata (Nowak et al. 2006; WHO 2016a).

The potential effect of greenness may be related to a combination of, and interactions between, the factors described above. For instance, parks or private or community gardens may offer places for physical activity and social interaction, as well as offering quiet places away from the intensity of traffic and crowds, which may both contribute to reduced stress, supporting health-promoting behaviors, and in the longer run, improved health.

1.4 RESEARCH GAPS

The study of greenness and health outcomes has been growing as a research field in recent years. Several experimental studies have shown positive short-term effects of greenness exposure, and observational studies have found associations between long-term greenness exposure and both physical and mental health outcomes. Taken together, this seems to point in the direction of greenness being beneficial for urban public health. Still, the majority of studies available today are cross-sectional, and with limited control for potential confounding by socio-demographic and socio-economic factors. The evidence from previous research is inconclusive concerning the long-term effects of greenness exposure on physical activity patterns, adiposity, and hypertension, and whether associations with general and mental health are similar across geographical areas. Moreover, there is limited knowledge on different effects in subgroups, and the effect of greenness in relation to other environmental exposures such as air pollution, transportation noise and blue space.

2 AIMS

The primary objective of the doctoral project was to investigate associations between residential greenness and physical activity, adiposity measures and hypertension, as well as general and mental health. The secondary objective was to investigate factors that may modify the relation between greenness and the outcomes: air pollution, transportation noise and blue space, as well as sociodemographic, behavioral, and socioeconomic factors. We expect the project to contribute to a better understanding of the factors affecting the greenness-health relationship, and further insight into the possible pathways involved.

The specific objectives of the individual studies were:

- To study the association between changing residential greenness exposure level, as a result of changing address, and changes in physical activity levels.
- To investigate the association between long-term residential greenness exposure and changes in weight and waist circumference, and development of overweight, obesity and central obesity.
- To examine the association between long-term greenness exposure and incidence of hypertension.
- To assess associations between residential exposure to green or blue aspects of the natural environment and physical as well as mental health.

3 MATERIAL AND METHODS

3.1 STUDY POPULATIONS

Papers I, II and III were based on cohorts from Stockholm County, Sweden, and include the Stockholm Public Health Cohort (SPHC) and The Stockholm Diabetes Prevention Program (SDPP). **Paper IV** used data from three cross-sectional studies – the Scania Public Health Survey (PHS), the Health Survey of Catalonia (ESCA) and the “Understanding Society” UK Household Longitudinal Survey (UKHLS) – conducted in Scania/Sweden, England and Wales/UK, and Catalonia/Spain respectively.

3.1.1 The Stockholm Public Health Cohort

The Stockholm Public Health Cohort (SPHC) is a large population-based cohort based on the Stockholm County Council public health surveys, which were initiated with the purpose of studying determinants of health and burden of disease (Svensson et al. 2013). Respondents to the surveys were selected randomly in 2002, 2006 and 2010 from Statistics Sweden’s register of the total adult Stockholm population, stratified by residential municipality. Participants were followed up every four years with questionnaire-based surveys. The study population in **Paper I** was based on the surveys from 2010 and 2014, including responses from 49 133 individuals (response rate of 67%). Participants with incomplete physical activity data (n=1 072) and residential location information (n=1 694), as well as participants with inaccurate area-based information (n=3 730) and individuals who reported to be confined to bed at both occasions (n=26) were excluded, resulting in a final analytical sample of 42 611 participants.

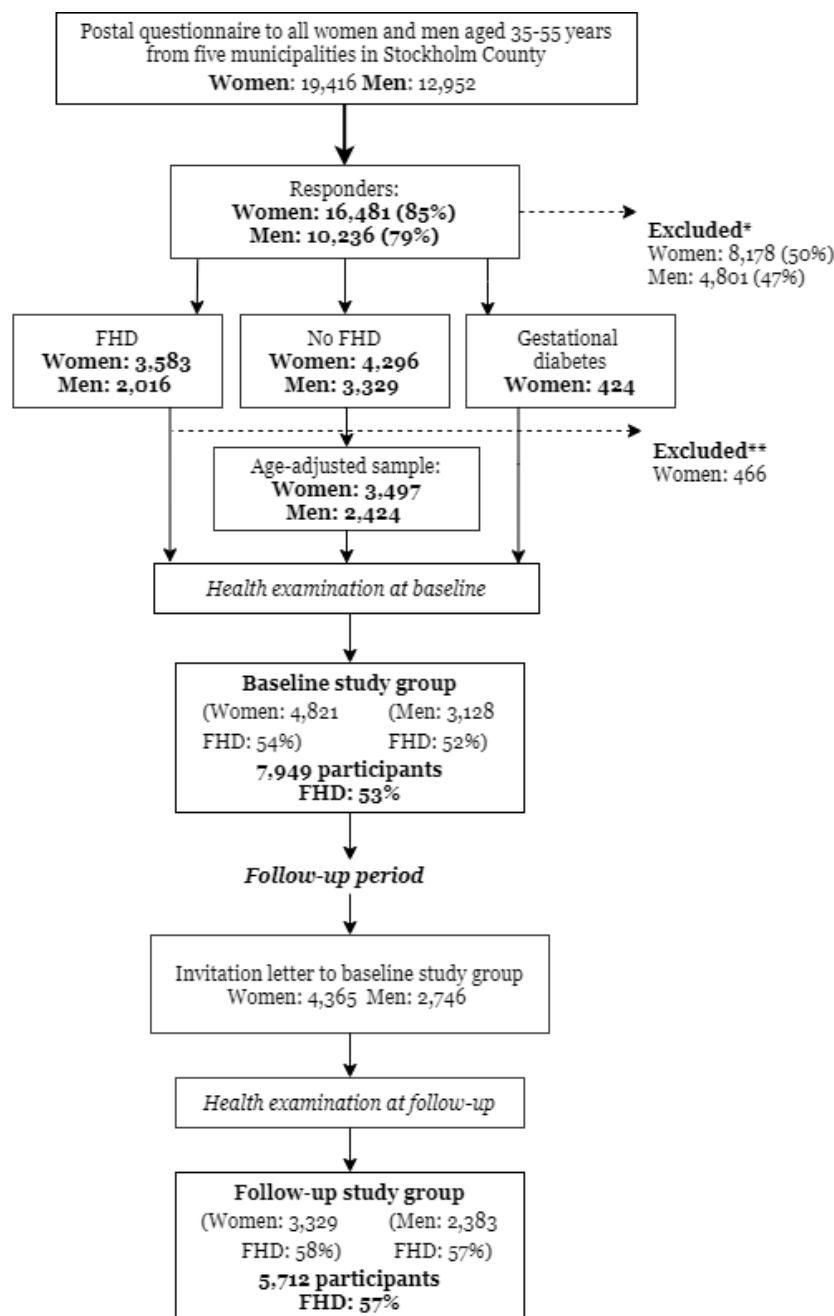
3.1.2 The Stockholm Diabetes Preventive Program

The Stockholm Diabetes Prevention Program (SDPP) was originally designed to study risk factors and prevention methods for type 2 diabetes (Andersson et al. 2002; Stjernschantz Forsberg et al. 2016). Thus, by design, approximately half (53%) of the participants had at least one first-degree relative (mother, father or sibling) or two second-degree relatives (grandparent, uncle or aunt) with diabetes, whereas the other half had no relatives with diabetes.

At recruitment in 1992–1998, all individuals aged 35–55 years residing in five municipalities in Stockholm County (Upplands Bro, Upplands Väsby, Sigtuna, Värmdö and Tyresö), were invited to participate in the baseline survey (Figure 1). Individuals already diagnosed with diabetes, with unclear diabetes heredity, or born outside Sweden were excluded. After matching the study population based on age and sex, 7 949 participants remained and constituted the baseline study group.

After an average of 9 years, in 2002–2007, 7 111 individuals who were still alive and residing in Stockholm County were invited to participate in the follow-up survey. Of these, 5 712 individuals (80% of those invited) completed the follow-up survey. Both the baseline and

follow-up clinical examinations were performed by trained nurses, who measured weight, height, waist circumference and blood pressure. Questionnaires at the baseline and follow-up examinations included questions on overall health status and health-related behaviors. In **Paper II**, participants were included in the study if they had complete address data, complete data on baseline and follow-up anthropometric variables and complete data on important covariates, resulting in an analytical sample of 5 126 individuals. In **Paper III**, the participants with complete exposure and co-variate and information, and who had not been diagnosed with hypertension or a related condition at recruitment, constituted the analytical sample of 4 623 individuals.



FHD — family history of diabetes

*Excluded because of diabetes (1.5% women and 2.5% men), foreign origin (7.6% women and 2.1% men), unclear FHD (28.5% women and 27.4% men) and insufficient FHD (9.9% women and 15.0% men)

**Excluded during the matching procedure

Figure 1. The Stockholm Diabetes Prevention Program.

3.1.3 The Scania Public Health Survey, the Health Survey of Catalonia and the “Understanding Society” UK Household Longitudinal Survey

Paper IV is a meta-analysis including three European cross-sectional study populations: the Public Health in Scania survey (“Folkhälsa i Skåne”; PHS); the General Population Sample of the United Kingdom Household Longitudinal Survey (UKHLS); and the Health Survey of Catalonia (“Enquesta de salut de Catalunya”; ESCA).

We identified three datasets that were derived from surveys conducted during the same period. The PHS is a cross-sectional county-wide survey that is repeated every four years. We used the most recent wave of the PHS, which was administered between October 2012 and March 2013 (n=28 029). The UKHLS is a longitudinal panel survey with yearly data collection. We used wave 4, which was administered between January 2012 and January 2014 (n= 47 071). The ESCA survey is conducted every six months. We used the waves 4, 5, 6 and 7, which were conducted in 2012 and 2013 (n=7 399). More information about survey design, sampling strategy and interview methods can be found in Fridh et al. (2013), Generalitat De Catalunya Departament De Salut (2012) and University of Essex and Institute for Social and Economic Research (2019).

In order to estimate green and blue space exposure based on the same data for all three datasets, we used the land use and land cover data set Copernicus Urban Atlas 2012 (UA2012) (European Environment Agency 2016). These data were available for urban areas of so-called Functional Urban Areas (FUA) and their surroundings, *i.e.* urban areas with >50 000 inhabitants. By using the spatial boundaries of the UA2012 data, we defined population subsets of each survey for the present analysis: 17 240 in PHS, 28 852 in UKHLS and 4 128 in ESCA. The total study population was 50 220 participants.

3.2 ENVIRONMENTAL EXPOSURES

3.2.1 Residential greenness

In **Papers I–III**, residential greenness exposure was estimated using the vegetation index NDVI (Normalized Difference Vegetation Index) for Stockholm County. These data were obtained from Landsat 5 TM and Landsat 8 composite images during the growing season (May 1 to September 30) for the years 1990–2016 at a 30x30 m resolution.

In **Paper I**, the exact residential addresses were not available because of confidentiality. Greenness was therefore estimated within the SAMS geographical area (Small Areas for Market Statistics) (Statistics Sweden 2017) that the participants were residing in. SAMS were developed by Statistics Sweden to represent socio-demographically homogeneous areas of 1,000–2,000 inhabitants, and typically constitute neighborhood or blocks. The SAMS size vary considerably, depending on the population density, but in Stockholm County, approximately 75% of the SAMS are around 1 km². From each geographical midpoint (centroid) of the SAMS, circular buffer zones of 1 km and 2 km radii were defined, and the average NDVI was calculated for land areas within the buffers.

In **Papers II** and **III**, average NDVI values were calculated for land areas surrounding the participant's residential addresses, using 100 m, 250 m, and 500 m radii buffers (in **Paper III**, only 250 and 500 m buffers were used). Because of the risk of cloud contamination and atmospheric effects resulting in underestimated NDVI values for particular years and locations, NDVI levels are estimated for the years of interest using robust regression based on the entire time period 1990–2016, and thereafter replacing the values deviating >-0.1 from the median NDVI for each address point with the estimated values.

In **Paper II** and **III**, the residential history, including duration of residence at each address was taken into account. Time-Weighted Average (TWA) NDVI exposure was calculated, using information on addresses and date of address change during follow-up, obtained from the Swedish Population Register through the Swedish Taxation Authority. In **Paper III**, time-weighted average exposure was calculated for exposure time windows of 5 and 10 years preceding the incidence of hypertension. For exposure before 1990, we assumed the NDVI level to be the same as in 1990. In addition, participants whose address information was missing in the beginning of the exposure period, *e.g.* before 1988, we assumed the addresses to be the same as in the first year with available address information. A small number of participants had missing address coordinates for some exposure time windows. We excluded participants with more than 20% missing exposure information from the analyses in order to reduce the uncertainty in the exposure assessments.

In **Paper IV**, different greenness measures were used. First, satellite-derived NDVI data at 250 m resolution were obtained from MODIS/Terra Vegetation Indices 16-Day L3 (Didan 2015) for the summer season in 2012. The median NDVI for 300 and 1000 m radii buffers around each residential geolocation was calculated for each respondent. Second, land cover data from Urban Atlas 2012 (European Environment Agency 2016) was used to create urban green exposure variables. Two groups of greenness variables were used: one classified as “urban green space” (including *e.g.* urban parks), and another one classified as “peri-urban green space” (including “pastures”, “forests” and “herbaceous vegetation association”) (European Environment Agency 2016). For each 300 and 1000 m radii buffers around residential addresses, we calculated the proportions of urban green space and peri-urban green space separately. Third, in this study we also used proximity metrics in the form of Euclidean distances between residential addresses and the nearest urban green space (defined as the Urban Atlas 2012 land class “urban green space”).

3.2.2 Air pollution

In **Papers II** and **III**, nitrogen oxides, NO_x , was used as a proxy for traffic-related air pollution exposure. Nitrogen dioxide (NO_2) is harmful to the airways, and NO_2 as well as NO_x ($\text{NO} + \text{NO}_2$) have repeatedly been associated with several health effects in population studies (Faustini et al. 2014; WHO 2006). NO_x is formed in all combustion processes including those in motor vehicles, together with other toxic compounds. Long-term exposure to NO_x (or NO_2) from road traffic has thus often been interpreted to represent the exposure to all air pollutants from road traffic, including both exhaust and non-exhaust compounds. We

have used modeled traffic-NO_x as a proxy for long-term exposure to all compounds from road traffic. Annual average concentrations of NO_x were estimated based on a Gaussian air-quality dispersion model and a wind model, both of which are part of the Airviro Air Quality Management system (SMHI 2020), and reflect mainly local sources of NO_x (Gruzieva et al. 2012; Segersson et al. 2017). Time Weighted Average (TWA) measures were calculated; in **Paper II** for the follow-up period, and in **Paper III** in exposure windows of 5 and 10 years preceding an incident case of hypertension, or, if none, preceding the follow-up examination.

In **Paper IV**, land cover data from Urban Atlas 2012, containing the land classes “fast transit roads” and “other roads”, was combined and used. Since air pollution and noise exposure data were not available for the entire study area, areas classified as roads served as a proxy of air and noise pollution and potentially other stressors or pollutants.

3.2.3 Transportation noise

Papers II and **III** included assessment of transportation noise exposure based on a methodology described in detail in Pyko et al. (2018). Individual-level road traffic and railway noise exposure was assessed using a noise database. The database was based on geographic information on sources and factors affecting noise levels and dispersion such as topography/terrain, buildings, the amount of vehicles on the roads and the proportion of heavy vehicles, road speed limits and different types of trains on different railway segments, obtained from different authorities and agencies. Annual averages of the 24-hour A-weighted equivalent continuous sound levels ($L_{Aeq,24h}$) at the façade at individual addresses were modelled based on a simplified version of the Nordic prediction method. Then, the $L_{Aeq,24h}$ -levels were re-calculated to day-evening-night levels (L_{den}), by using penalties for exposure occurring during evening and night, to take into account higher noise sensitivity during night-time, following a methodology used by Pyko et al. (2017). Aircraft noise exposure (in L_{den}) was estimated from geographic information on noise contours, calculated by the Integrated Noise Model (INM version 6.1) (Olmstead et al. 2002) and derived from flight radar tracks obtained from Swedavia, which owns and operates the two major airports in Stockholm County (Bromma and Arlanda). By spatially linking the noise levels to residential addresses, the individual noise exposure could be estimated. Modeled levels below 35 dB L_{den} were considered to be uncertain and set to 35 dB L_{den} . In **Paper II**, we calculated the TWA noise exposure levels during follow-up based on the residential history. In **Paper III**, we calculated TWA exposures for 5 and 10 years preceding an incident case of hypertension, or, if none, preceding the follow-up examination.

3.2.4 Blue space

In **Papers II** and **III**, blue space exposure, *i.e.* residential proximity to water, was assessed by calculating the Euclidean distance between the residential addresses and the nearest body of water of at least 500 m² (lakes and the sea) or at least 6 m wide (rivers and streams). We used Geographic Information System (GIS) software and land use data from the Swedish Mapping, Cadastral and Land Registration Authority (Lantmäteriet 2018). In **Paper IV**, blue

space exposure was assessed both as an area-based and distance metric. We used land cover data from the Urban Atlas 2012 (European Environment Agency 2016) to calculate proportions within the 300 and 1000 m radii buffers, and to calculate the Euclidean distance to the nearest body of water of at least 1 ha and 10 m wide.

3.3 COVARIATES

Based on previous studies, we identified potential confounders likely to affect the relationship between exposure to natural environments and the outcomes of interest in all studies. In **Paper I**, the individual-level baseline covariates sex, age and education were obtained from register data from Statistics Sweden and linked to the self-reported questionnaire information through personal identification numbers. In **Papers II** and **III**, demographic and health- and lifestyle-related parameters such as sex, age, physical activity, tobacco and alcohol consumption, dietary habits, psychological distress, shift work, job strain and individual socioeconomic status (SES, education level and type of occupation) were collected through questionnaires and interviews at baseline. In **Paper IV**, individual-level covariates were collected from questionnaires and interviews and included sex, age, country of birth, educational level, work status, marital status, household composition and household income (for PHS and UKHLS adjusted for household composition). For the Scania survey, information on employment, income and healthcare was obtained from Swedish registries and linked to the questionnaire-derived data.

In **Papers I–III**, we assessed contextual socioeconomic status by using the mean income (in SEK, Swedish krona) of the SAMS the individual participant was residing in at baseline, obtained from Statistics Sweden for the year 2009 (Statistics Sweden 2017). In **Paper IV**, we assessed contextual socio-economy through mean income in SAMS for the year 2009 for Scania (Statistics Sweden 2017), the deprivation indicator Carstairs for the UKHLS (Wheeler 2019) and an inequality index based on unemployment and illiteracy rates from the 2011 census for ESCA.

In **Paper IV**, we harmonized categorization of our exposure variables and covariates in order to have enough numbers in each category for all territories. This procedure was guided by the results of empirical research (Elliott et al. 2020).

3.4 HEALTH OUTCOMES

3.4.1 Physical activity

In **Paper I**, self-reported physical activity was assessed using the validated Physical Activity Questionnaire (Norman et al. 2001; Orsini et al. 2008). Walking/cycling and exercise were assessed separately, and the participants reported their estimated average daily behavior during the past 12 months, considering the week variability and seasonality. Walking/cycling had six response categories (<1 hour/day – >5 hours/day) and exercise had seven response categories (hardly ever – >5 hours/week). A change (decrease or increase) by at least one category between 2010 and 2014, was considered a change in physical activity level.

3.4.2 Overweight and obesity

In **Paper II**, information on weight, height and waist circumference was collected at baseline and follow-up clinical examinations in the Stockholm Diabetes Prevention Program. From these data, Body Mass Index (BMI) was calculated as weight in kilograms/height in m², with the cut-offs ≥ 25 to define overweight and ≥ 30 to define obesity (WHO 2018c). Central obesity was defined as having a waist circumference of ≥ 88 cm for women and ≥ 102 cm for men; cut-offs that have been used in the diagnostic criteria for metabolic syndrome (Grundy et al. 2005). Moreover, these cut-offs are believed to be associated with increased risk for development of metabolic complications, such as diabetes and cardiovascular disease (NHLBI 1998).

3.4.3 Hypertension

In **Paper III**, information from three different sources was combined to identify incident cases of hypertension. First, information on diagnosed hypertension was collected through the National Patient Register; if an individual had a diagnosis of hypertension (ICD-9 codes 401X before 1998 and ICD-10 codes I10X from 1998), they were identified as a case. Second, blood pressure was measured once, after five minutes of rest and in a sitting position, with a hand aneroid sphygmomanometer, Conformité Européenne, CE0123 (Welch Allyn, NY, USA). Individuals with measured systolic blood pressure ≥ 140 mmHg and a diastolic blood pressure ≥ 90 mmHg at the baseline and follow-up examinations, were considered hypertensive, following the WHO definition of hypertension grade I (Chalmers et al. 1999). Third, an individual who reported usage of antihypertensive treatment or doctors' diagnosis of hypertension during the last 10 years in the follow-up questionnaire, was considered a case.

3.4.4 General and mental health

In **Paper IV**, two self-reported measures of health were studied in relation to different metrics of natural space. First, general health was derived from the Short Form 1 (SF-1), the first item of the Short-Form Health Survey (SF-36) (Ware and Sherbourne 1992). SF1 is formulated as a question, "In general, would you say your health is...?", with responses following a 5-point Likert scale: (1) excellent, (2) very good, (3) good, (4) fair and (5) poor. We generated a binary variable following the standard procedure, and defined scores 1, 2 and 3 as "good health", and 4 and 5 as "poor health" for UKHLS and ESCA. For Scania, however, the wording was different: 1 (very good), 2 (good), 3 (fair), 4 (poor) and 5 (very poor), and we subsequently defined 1–2 as "good health", and 3–5 as "poor health".

Second, mental health was derived from the 12-item General Health Questionnaire (GHQ-12), a short form of the 60-item GHQ (Goldberg and Williams 1988). Based on the 12 items, a single scale may be generated by recoding scores of 1 and 2 to 0, and 3 and 4 to 1. The scores are summed, which generates a scale running from 0 (the least distressed) to 12 (the most distressed). Based on this scale, we generated a binary variable with thresholds determined for each geographical area, following the standard approach of setting the

threshold at the mean score of the sample (Goldberg et al. 1998). The mean scores for GHQ in the study populations were 1.41, 1.86, and 0.86, respectively, for PHS, UKHLS and ESCA. Based on the means, we developed survey-specific thresholds to define “caseness”, *i.e.* to identify individuals “at risk of poor mental health”: ≥ 2 (PHS); ≥ 3 (UKHLS); and ≥ 1 (ESCA). We also conducted sensitivity analysis using the same caseness criterion for all datasets, defining ≥ 3 as “at risk of poor mental health”, which has been used in previous studies.

3.5 STATISTICAL ANALYSIS

In **Paper I**, we analyzed changes in physical activity levels separately for walking/cycling and exercise in relation to change in neighborhood greenness exposure following residential relocation between 2010 and 2014. A change in greenness exposure was defined as changing NDVI level by one quartile; to a less green area, the same quartile, or change to a greener area. We performed multinomial logistic regression analyses to generate Odds Ratios (ORs) and 95% confidence intervals (CIs). Furthermore, we performed analyses stratified by sex, age, education and area-based income.

In **Paper II**, we assessed the long-term associations between residential greenness exposure and change in waist circumference and weight as well as incidence of overweight, obesity and central obesity. The greenness exposure, NDVI, was scaled to interquartile range (IQR), and associations with the outcomes modelled in relation to one IQR increase in NDVI. Initially, we used Pearson chi-square tests for categorical variables and t-tests for continuous variables to analyze associations between background characteristics of the SDPP cohort in relation to NDVI exposure (below or above median) within the 500 m buffer around each residential address. The continuous outcomes (change per year in waist circumference and weight) were analyzed through linear regression models to generate beta (β) coefficients and 95% CIs. Associations with the binary outcomes (overweight, obesity and central obesity), were modelled using Poisson regression to generate incidence rate ratios (IRR) and 95% CIs. In the Poisson regression models, we used follow-up time as a proxy for person-time, by using the Stata command *exposure* in the models. A stepwise regression modelling process was applied. First, we included covariates based on change-in-estimates criteria: covariates resulting in a $>5\%$ change in estimates were retained in the models. Second, covariates associated at the 0.1 significance level were included in the final model.

Furthermore, we analyzed potential effect modification by introducing interaction terms with NDVI and the covariates to the models. Sex was identified as an effect modifier at an early stage, and all models therefore included interaction terms with NDVI and sex, and all results reported were sex specific. Further interaction analysis included evaluating models with and without interaction terms using f-statistics. We also assessed NDVI in combination with other environmental exposures by analyzing change in waist circumference at different combinations of high or low exposure to NO_x, distance to blue space and road traffic, railway and aircraft noise. Moreover, we conducted sensitivity analyses to assess the robustness of the associations. We restricted the sample to those who did not change their address during the

follow-up period, and to those without diabetes heredity. We also included additional adjustments for contextual confounding (SAMS mean income), and baseline waist circumference, respectively. Finally, we assessed the assumption of linearity between NDVI exposure and waist circumference as well as weight change. We conducted restricted cubic spline (RCS) analyses with three knots positioned at the 10th, 50th and 90th percentile, equivalent to the values 0.42, 0.50 and 0.57 on the NDVI scale in the 500 m radius buffer. We evaluated the models with and without the RCS through the likelihood ratio test.

In **Paper III**, we investigated incidence of hypertension in relation to greenness exposure during 5 and 10 years preceding hypertension diagnosis. Residential greenness exposure was defined as NDVI, which was modelled as a continuous variable scaled to the interquartile range (IQR) values, and as a categorical variable with NDVI categorized into quartiles. We analyzed differences in background characteristics at baseline in relation to whether participants were included or excluded in the study, developed hypertension or not, and had baseline NDVI exposure below or above the median, respectively. We used Cox proportional hazards regression models to generate Hazard Ratios (HRs) and 95% CIs, with age as the underlying time scale. Person-time at risk was defined as the time between the baseline investigation and the first occurring diagnosis of hypertension, a hypertension-related disease diagnosis, or the follow-up investigation, if the participants remained normotensive. Model specification was based on a stepwise backward modelling approach, retaining covariates associated at the 90% confidence level ($p < 0.1$) when included in models. Focusing on the 5-year exposure, effect modification was investigated by introducing interaction terms with NDVI and individual and environmental covariates. Statistical significance of models with and without interaction term was evaluated by using likelihood-ratio tests ($p < 0.1$ defined as significant). We further performed sensitivity analysis, also focusing on the 5-year exposure. We ran models with additional adjustment (physical activity, tobacco use, baseline BMI and waist circumference as well as baseline municipality of residents, respectively). Furthermore, we excluded the covariate psychological distress. We also investigated whether source of diagnosis information influenced the association by analyzing two sub-groups. In the first subgroup, only individuals identified as hypertensive via measurements at the follow-up investigation were included. In the second group, only those identified via questionnaires (self-reported doctor's diagnosis of hypertension or anti-hypertensive treatment) or by the national patient register, were included. We also assessed potential misclassification of exposure by restricting the sample to participants with complete exposure data 10 years before hypertension diagnosis.

In **Paper IV**, we investigated associations between different metrics of green and blue spaces, and self-reported general and mental health through meta-analysis of three cross-sectional datasets. We used multiple imputation by chained equations (MICE) to impute covariate data considered missing at random (MAR). In brief, this imputation method is based on two phases. First, a set of imputation models is generated, one for each variable with missing values, and based on the distribution of variables with complete information. Second, the estimates from the imputation models are combined to generate an overall estimate. Multiple

imputation was performed only for individual covariates, not for exposure or outcome information. To evaluate the performance of the imputation, we compared estimates from regression models including imputed values, and models not including imputed values.

We used logistic regression models to estimate the associations between three sets of green and blue space metrics, and the outcomes of interest, by generating Odds Ratios (ORs) and 95% CIs. All models were run with three levels of adjustment: first without adjustment for any covariates, then with adjustment for all individual-level covariates, and then for individual- and area-level covariates. Furthermore, socio-economic status was investigated through stratified analyses. Models were run stratified on a) individual SES (household income adjusted for household composition) and b) area-level SES.

Finally, meta-analysis to obtain pooled estimates was conducted using random-effects models. Random-effects models are based on the assumption that there are differences in the effect among the studies included, and that the studies are a random sample of possible studies. To assess the heterogeneity between the studies, τ^2 was estimated using the DerSimonian-Laird estimator, and the heterogeneity statistics H , I^2 and Q were calculated.

In **Paper I**, statistical analyses were performed in IBM SPSS Statistics version 23 (IBM Corporation 2016). In **Papers II and III**, Stata All statistical analyses were performed using Stata/SE 14.2 (StataCorp 2016) and 14.1 (StataCorp 2015), respectively. In **Paper IV**, statistical analysis for the individual studies were performed using Stata/SE 14.1 for the PHS and ESCA data, and R software 3.5.1 (R Core Team 2013) for the UKHLS data. The meta-analysis was performed using R software 3.5.1. Greenness and blue space exposure assessments were performed using ArcMap 10.4.1 (ESRI 2017) in **Papers I–III**, and ArcGIS 10.1 (ESRI 2012) and R software 3.5.1 (R Core Team 2013) in **Paper IV**.

3.6 ETHICAL CONSIDERATIONS

The data collection, management, linkage with register data and spatial linkage with environmental exposure data, storage and analyses for the studies included in this thesis were approved by ethical review boards. **Paper I**, Dnr. 2006/1112-31, 2012/1812-32 and 2016/749-32, by the Regional Ethical Review Board, Stockholm. **Papers II and III**, Dnr. 2009/2166-31/5 and 2018/2064-32, by the Regional Ethical Review Board, Stockholm. **Paper IV**, Dnr. 2015/313 and 2018/315 for the PHS data, by the Regional Ethical Review Board, Lund, and reference number Oct17/D/142 for the UKHLS data, by University of Exeter Medical School Research Ethics Committee. For the ESCA data, no ethical permission for analysis of secondary data was required.

4 RESULTS

4.1 PHYSICAL ACTIVITY

In **Paper I**, we studied changes in physical activity in relation to changes in neighborhood greenness. Of the 42 611 individuals who formed the analytical sample, 2 074 (5%) individuals moved to a less green area between 2010 and 2014, and 2 141 (5%) moved to a greener area. The baseline walking/cycling levels were: 6% hardly ever, 20% <20 min/day, 43% 20–40 min/day, 19% 40–60 min/day, 9% 1–1.5 h/day, and 4% >2 h/day. The baseline exercise levels were: 21% hardly ever, 18% <1 h/week, 28% 1–2 h/week, 16% 2–3 h/week, 8% 3–4 h/week, 4% 4–5 h/week, and 5% >5 h/week.

The two aspects of physical activity were differently related to changes in neighborhood greenness following residential relocation. Regarding walking/cycling, moving to a less green area was associated with increased walking/cycling, whereas moving to a greener area was associated with decreased walking/cycling, compared to staying at the same greenness level (Table 2). Regarding exercise, moving to a less green area was associated with decreased exercise, and moving to a greener area was associated with an increased risk of decreased exercise as well as a decreased risk of increased exercise, compared to staying at the same greenness level.

In the stratified analysis, women appeared to be more likely to increase walking/cycling after moving to a greener area, compared to men. Moreover, individuals below 56 years of age appeared to be more likely to decrease their walking/cycling after moving to a greener area, than among individuals aged 56 years or more. Concerning education, the pattern was less clear. The odds of increasing walking/cycling after moving to a greener area were higher among individuals with high education, but the odds of decreasing walking/cycling after moving to a greener area were also higher among individuals with high education, than among individuals with low education. With regards to exercise, differences were found for age only. Individuals below 56 years of age appeared more likely to decrease exercise levels both after moving to greener and less green area, than individuals aged 56 years or more.

Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for change in physical activity level in relation to changing greenness levels following residential relocation (N=42 611).

	Walking/cycling		Exercise	
	Decrease	Increase	Decrease	Increase
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Moved to less green	1.07 (0.96; 1.19)	1.26 (1.13; 1.41)	1.22 (1.09; 1.36)	1.11 (0.99; 1.24)
Moved to greener	1.42 (1.28; 1.58)	1.09 (0.97; 1.22)	1.25 (1.12; 1.38)	0.89 (0.79; 0.99)

Adjusted for sex, age, education and mean area-based income.

Reference outcome variable = stable walking/cycling/exercise, reference exposure variable = stable greenness

4.2 Overweight and obesity

In **Paper II**, we studied change in weight and waist circumference, as well as development of overweight, obesity and central obesity in relation to long-term greenness exposure, defined as time-weighted average NDVI in 100, 150 and 500 m radii buffers around residential addresses. The 5 126 subjects from the SDPP cohort were followed in average 8.9 years.

In the fully adjusted models, we did not observe an association between NDVI and weight development in women or in men, and regardless of buffer size (Table 2). Regarding the risk of overweight in relation to increased NDVI exposure, a statistically significant increased risk was observed for men in the fully adjusted model in the 100 m buffer (IRR 1.16, 95% CI 1.00; 1.34 per IQR). We did not observe any other associations between NDVI exposure and incidence of overweight or obesity.

Increased residential NDVI was associated with a reduced increase in waist circumference in women in all buffer sizes. The largest reduction was observed for the 500 m buffer (-0.11 cm per year, 95% CI -0.14; -0.08 cm per one IQR increase in NDVI) (Table 3). No association between greenness exposure and waist circumference was observed among men. Regarding central obesity, we observed an association in women and in the 500 m buffer (IRR 0.88, 95% CI 0.79; 0.99 per IQR), but not in men, and not in other buffer sizes.

Table 2. NDVI exposure in 100 m, 250 m or 500 m radii buffers around residential addresses during follow-up, in relation to change in weight and waist circumference (beta-coefficients (β) and 95% confidence intervals (95% CI); N=5 126).

Continuous, per one IQR ^c increase in NDVI	Weight gain (kg/year)		Waist circumference increase (cm/year)	
	Model 1 ^a	Model 2 ^b	Model 1 ^a	Model 2 ^b
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
100 m radius				
females	-0.02 (-0.05; 0.01)	-0.01 (-0.04; 0.02)	-0.06 (-0.09; -0.02)	-0.06 (-0.10; -0.02)
males	-0.01 (-0.04; 0.03)	0.01 (-0.03; 0.04)	-0.04 (-0.09; 0.00)	-0.01 (-0.05; 0.03)
250 m radius				
females	-0.03 (-0.06; 0.00)	-0.02 (-0.05; 0.01)	-0.07 (-0.10; -0.03)	-0.08 (-0.11; -0.04)
males	-0.01 (-0.04; 0.03)	0.00 (-0.03; 0.04)	-0.03 (-0.07; 0.01)	-0.01 (-0.05; 0.03)
500 m radius				
females	-0.03 (-0.06; 0.00)	-0.02 (-0.05; 0.01)	-0.09 (-0.13; -0.06)	-0.11 (-0.14; -0.08)
males	-0.00 (-0.04; 0.03)	0.01 (-0.03; 0.04)	-0.02 (-0.06; 0.02)	-0.00 (-0.04; 0.03)

^a Adjusted for age.

^b Adjusted for age, alcohol consumption, tobacco use, psychological distress, shift work, aircraft noise, railway noise and distance to blue space.

^c NDVI IQR 100 m: 0.108, 250 m: 0.085, 500 m: 0.072.

Table 3. Incidence of overweight, obesity and central obesity during follow-up in the study cohort in relation to NDVI exposure in 100, 250 or 500 m radii buffers (Incidence Risk Ratios (IRR) and 95% Confidence Intervals (95% CI)).

Overweight (n=2 540) ^a		Obesity (n=4 577) ^b		Central obesity (n=4 340) ^c	
Continuous NDVI, per one IQR increase ^d	Model 1 ^e	Model 2 ^f	Model 1 ^e	Model 2 ^f	Model 2 ^f
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
100 m radius					
females	0.94 (0.82; 1.07)	0.96 (0.83; 1.09)	1.01 (0.84; 1.22)	1.02 (0.85; 1.23)	0.93 (0.83; 1.04)
males	1.12 (0.98; 1.29)	1.16 (1.00; 1.34)	0.99 (0.83; 1.19)	1.01 (0.84; 1.22)	0.83 (0.71; 0.96)
250 m radius					
females	0.92 (0.81; 1.05)	0.94 (0.83; 1.07)	1.03 (0.86; 1.22)	1.03 (0.86; 1.24)	0.89 (0.80; 0.99)
males	1.12 (0.98; 1.28)	1.14 (1.00; 1.32)	1.02 (0.86; 1.21)	1.04 (0.87; 1.24)	0.83 (0.72; 0.96)
500 m radius					
females	0.96 (0.85; 1.09)	0.98 (0.86; 1.11)	1.05 (0.89; 1.25)	1.05 (0.88; 1.26)	0.88 (0.79; 0.97)
males	1.09 (0.96; 1.25)	1.12 (0.97; 1.28)	1.05 (0.89; 1.23)	1.06 (0.89; 1.26)	0.87 (0.76; 1.00)

^a Excluding those with BMI ≥ 25 at baseline. ^b Excluding those with BMI ≥ 30 at baseline.

^c Excluding the women with waist circumference ≥ 88 cm and men with waist circumference ≥ 102 cm at baseline.

^d NDVI IQR 100 m: 0.108, 250 m: 0.085, 500 m: 0.072.

^e Adjusted for age.

^f Adjusted for age, alcohol consumption, tobacco use, psychological distress, shift work, aircraft noise, railway noise and distance to blue space.

4.3 HYPERTENSION

In **Paper III**, we studied the incidence of hypertension in relation to time-weighted average NDVI exposure during 5 and 10 years preceding diagnosis of hypertension. In the study population consisting of 4 623 individuals, the 5-year TWA exposure period gave rise to 1 212 hypertension cases during 38 084 person-years, and the 10-year TWA exposure period gave rise to 1 225 hypertension cases during 37 802 person-years. In the fully adjusted model, we observed a statistically significant association between increased greenness exposure in the 5-year exposure period and reduced hypertension risk (HR 0.88, 95% CI 0.80; 0.97, per IQR increase in NDVI) (Table 4). The NDVI exposure 10 years preceding the hypertension diagnosis was not associated with hypertension risk (HR 1.00, 95% CI 0.91; 1.10, per IQR increase).

Table 4. Risk of hypertension in relation to time-weighted average (TWA) NDVI in 500 m radii buffers during 5 and 10 years preceding the incidence of hypertension.

5 years TWA preceding hypertension incidence			10 years TWA preceding hypertension incidence		
Person-years: 38 084			Person-years: 37 802		
Number of cases: 1 212			Number of cases: 1 225		
	NDVI as continuous (per one IQR increase)	NDVI as categorical (quartiles)	NDVI as continuous (per one IQR increase)	NDVI as categorical (quartiles)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
MODEL 1 ^a	1.08 (1.00; 1.16)	1 (ref)	1.14 (1.06; 1.23)	1 (ref)	
		2 0.94 (0.80; 1.10)		2 1.13 (0.95; 1.33)	
		3 1.00 (0.85; 1.17)		3 1.11 (0.94; 1.31)	
		4 1.12 (0.96; 1.31)		4 1.31 (1.11; 1.53)	
MODEL 2 ^b	1.10 (1.03; 1.19)	1 (ref)	1.17 (1.09; 1.26)	1 (ref)	
		2 0.97 (0.82; 1.14)		2 1.17 (0.99; 1.39)	
		3 1.04 (0.89; 1.23)		3 1.17 (0.99; 1.38)	
		4 1.18 (1.01; 1.39)		4 1.39 (1.18; 1.64)	
MODEL 3 ^c	0.88 (0.80; 0.97)	1 (ref)	1.00 (0.91; 1.10)	1 (ref)	
		2 0.80 (0.68; 0.96)		2 1.03 (0.86; 1.23)	
		3 0.81 (0.67; 0.96)		3 0.95 (0.79; 1.15)	
		4 0.81 (0.67; 0.99)		4 1.02 (0.84; 1.25)	

^a Adjusted for sex and diabetes heredity

^b Adjusted for sex, diabetes heredity, education, individual SES (occupation), psychological distress, area level mean income.

^c Adjusted for sex, diabetes heredity, education, individual SES (occupation), psychological distress, area level mean income, distance to blue space, road traffic and aircraft noise, NO_x

4.4 GENERAL AND MENTAL HEALTH

In **Paper IV**, we investigated self-reported general health in relation to green and blue spaces in a meta-analysis of three European cross-sectional studies. The total number of respondents that had residential geolocations within the limits of UA2012 land cover data to were 50 220 respondents (PHS n=17 240, UKHLS n=28 852 and ESCA n=4 128). The proportion of the respondents reporting being in good general health from SF1 was 73% in PHS and 79% in UKHLS and ESCA. Regarding mental health, 24% in PHS, 32% in UKHLS and 12% in ESCA were identified as being at risk of mental illness as indicated by GHQ-12.

The pooled estimates from meta-analysis provided little evidence of associations between exposure to residential greenness or blue space, and good general or mental health (Table 5 and 6). However, the meta-analysis of the fully adjusted estimates, indicated associations between measures of natural space and general health. Having 5–10% land use urban green in the 1000 m buffer (compared to <5%) was associated with lower odds of good general health (pooled estimate: OR 0.92, 95% CI 0.87; 0.98). Living more than 2.5 km from a river, (compared to <1 km) was associated with increased odds of good general health (pooled estimate: OR 1.09, 95% CI 1.02; 1.17). No statistically significant associations were found for mental health in the meta-analysis (Table 6).

Table 5. Results of regression analysis for SFI, predicting good general health, by survey and with summary estimates from meta-analysis.

Model	Predictor	Category or exposure increment	PHS ^b OR (95% CI)	UKHLS ^c OR (95% CI)	ESCA ^d OR (95% CI)	Pooled summary estimate OR (95% CI)
i ^a	NDVI in 1000 m buffer	per 0.1 increase	1.02 (0.96; 1.08)	1.01 (0.96; 1.06)	1.09 (0.97; 1.23)	1.02 (0.98; 1.05)
	Blue space in 1000 m buffer (ref. none)	some	0.98 (0.90; 1.07)	1.03 (0.96; 1.10)	1.04 (0.86; 1.26)	1.01 (0.96; 1.06)
ii ^a	Urban green space in 1000 m buffer (ref. 0%–5%)	5%–10%	0.89 (0.79; 1.00)	0.93 (0.86; 1.00)	1.01 (0.81; 1.25)	0.92 (0.87; 0.98)
		10%–100%	0.91 (0.81; 1.03)	0.94 (0.86; 1.03)	1.03 (0.70; 1.51)	0.93 (0.87; 1.00)
	Peri-urban green space in 1000 m buffer (ref. 0%–5%)	5%–10%	1.07 (0.94; 1.22)	1.03 (0.92; 1.16)	1.05 (0.76; 1.45)	1.05 (0.97; 1.14)
		10%–100%	0.96 (0.85; 1.09)	0.92 (0.84; 1.00)	1.11 (0.85; 1.43)	0.94 (0.88; 1.01)
	Blue space in 1000 m buffer (ref. none)	some	0.97 (0.89; 1.05)	1.03 (0.97; 1.10)	1.02 (0.84; 1.23)	1.01 (0.96; 1.06)
iii ^a	Distance to nearest urban green space (ref. 0 m–300 m)	300 m–1 km	0.97 (0.86; 1.09)	1.01 (0.94; 1.08)	0.89 (0.74; 1.07)	0.99 (0.93; 1.04)
		1 km–Inf.	1.00 (0.83; 1.20)	1.10 (0.94; 1.29)	0.86 (0.59; 1.25)	1.04 (0.93; 1.16)
	Distance to nearest coast (ref. 0 km–1 km)	1 km–5 km	0.97 (0.87; 1.09)	0.88 (0.73; 1.05)	0.91 (0.66; 1.24)	0.94 (0.86; 1.03)
		5 km–25 km	1.04 (0.92; 1.17)	0.98 (0.82; 1.18)	0.94 (0.68; 1.29)	1.01 (0.92; 1.11)
		25 km–50 km	1.16 (0.88; 1.53)	1.01 (0.85; 1.21)	0.78 (0.51; 1.19)	1.02 (0.86; 1.20)
	Distance to nearest lake (ref. 0 km–5 km)	50 km–Inf.	NA	0.92 (0.78; 1.10)	0.70 (0.42; 1.17)	0.90 (0.76; 1.06)
		5 km–15 km	0.97 (0.81; 1.15)	1.03 (0.97; 1.10)	1.29 (0.79; 2.09)	1.03 (0.96; 1.09)
	Distance to nearest river (ref. 0 km–1 km)	15 km–Inf.	0.99 (0.83; 1.19)	1.06 (0.92; 1.22)	1.30 (0.81; 2.11)	1.04 (0.94; 1.16)
		1 km–2.5 km	1.10 (0.99; 1.22)	0.99 (0.92; 1.06)	0.90 (0.72; 1.12)	1.01 (0.92; 1.11)
		2.5 km–Inf.	1.15 (1.03; 1.27)	1.07 (0.97; 1.17)	0.95 (0.71; 1.29)	1.09 (1.02; 1.17)

^a All models are adjusted for season of interview (except for in PHS), sex, age, nationality (born in the country of the survey, vs not), educational level, work status, marital status, household size, household income, area-based SES and proportion road area in exposure buffers.

^b Public Health in Scania Health survey, ^c United Kingdom Household Longitudinal Survey, ^d Survey of Catalonia (Enquesta de salut de Catalunya)

Table 6. Results of regression analysis for GHQ, predicting good mental health, by survey and with summary estimates from meta-analysis.

Model	Predictor	Category or exposure increment	PHS ^b OR (95% CI)	UKHLS ^c OR (95% CI)	ESCA ^d OR (95% CI)	Pooled summary estimate OR (95% CI)
i ^a	NDVI in 1000 m buffer	per 0.1 increase	1.04 (0.98; 1.10)	1.02 (0.98; 1.06)	1.07 (0.96; 1.18)	1.03 (1.00; 1.06)
	Blue space in 1000 m buffer (ref. none)	some	1.04 (0.95; 1.13)	1.02 (0.97; 1.08)	1.05 (0.89; 1.23)	1.03 (0.98; 1.08)
ii ^a	Urban green space in 1000 m buffer (ref. 0%–5%)	5%–10%	0.99 (0.87; 1.12)	1.10 (1.02; 1.18)	1.30 (1.08; 1.56)	1.10 (0.98; 1.24)
		10%–100%	1.00 (0.88; 1.12)	1.07 (0.99; 1.16)	1.26 (0.91; 1.74)	1.06 (0.98; 1.13)
	Peri-urban green space in 1000 m buffer (ref. 0%–5%)	5%–10%	1.14 (1.00; 1.30)	1.01 (0.91; 1.12)	1.28 (0.98; 1.68)	1.10 (0.97; 1.24)
		10%–100%	1.16 (1.02; 1.31)	1.03 (0.95; 1.12)	1.51 (1.21; 1.89)	1.19 (0.99; 1.42)
	Blue space in 1000 m buffer (ref. none)	some	1.03 (0.95; 1.11)	1.02 (0.96; 1.08)	1.01 (0.86; 1.18)	1.02 (0.97; 1.07)
iii ^a	Distance to nearest urban green space (ref. 0 m–300 m)	300 m–1 km	0.96 (0.85; 1.08)	0.99 (0.93; 1.06)	0.87 (0.74; 1.01)	0.96 (0.90; 1.03)
		1 km–Inf.	1.09 (0.90; 1.33)	0.92 (0.80; 1.05)	0.72 (0.54; 0.97)	0.92 (0.76; 1.11)
	Distance to nearest coast (ref. 0 km–1 km)	1 km–5 km	1.06 (0.94; 1.19)	0.95 (0.81; 1.12)	0.80 (0.61; 1.04)	0.96 (0.83; 1.11)
		5 km–25 km	0.97 (0.86; 1.10)	1.01 (0.86; 1.18)	0.81 (0.62; 1.07)	0.97 (0.88; 1.06)
		25 km–50 km	0.98 (0.73; 1.32)	0.94 (0.81; 1.10)	0.43 (0.31; 0.62)	0.75 (0.49; 1.16)
		50 km–Inf.	NA	0.95 (0.81; 1.10)	0.36 (0.24; 0.55)	0.60 (0.23; 1.53)
	Distance to nearest lake (ref. 0 km–5 km)	5 km–15 km	0.92 (0.77; 1.10)	0.97 (0.91; 1.03)	0.92 (0.60; 1.41)	0.96 (0.91; 1.02)
		15 km–Inf.	0.90 (0.75; 1.08)	0.90 (0.80; 1.02)	1.25 (0.81; 1.91)	0.92 (0.83; 1.02)
	Distance to nearest river (ref. 0 km–1 km)	1 km–2.5 km	0.94 (0.84; 1.05)	0.98 (0.92; 1.05)	0.96 (0.80; 1.16)	0.97 (0.92; 1.02)
		2.5 km–Inf.	0.91 (0.82; 1.01)	1.01 (0.93; 1.10)	1.02 (0.79; 1.31)	0.97 (0.90; 1.05)

^a All models are adjusted for season of interview (except for in PHS), sex, age, nationality (born in the country of the survey, vs not), educational level, work status, marital status, household size, household income, area-based SES and proportion road area in exposure buffers.

^b Public Health in Scania Health survey, ^c United Kingdom Household Longitudinal Survey, ^d Survey of Catalonia (Enquesta de salut de Catalunya)

4.5 SENSITIVITY ANALYSES

In **Papers II** and **III**, we investigated the consistency of our findings through further adjustment for individual and contextual covariates, omitting covariates from the models, and by restricting the analysis to study population subgroups.

In both **Papers II** and **III**, restricting the study population to those who were staying at the same address during follow-up resulted in a slightly stronger negative association between NDVI and change waist circumference, or hypertension risk, respectively. In **Paper II**, we did not observe meaningful changes in associations when analyzing the sub-group without diabetes heredity, when additionally adjusting for baseline waist circumference or for contextual SES (SAMS mean income). In **Paper III**, we did not observe any significant changes in estimates when additionally adjusting for baseline BMI, waist circumference, physical activity or residential municipality, or when we omitted psychological distress, respectively. However, we did observe that the source of information for case identification appeared influential; a more pronounced risk reduction was observed when analyzing the sub-group of hypertension cases identified from blood pressure measurements at the follow-up examination (HR 0.66, 95% CI 0.56; 0.77 per IQR increase in NDVI), but no association when focusing on cases identified from self-reported questionnaire data or from the national patient register (HR 1.10, 95% CI 0.97; 1.25). Finally, focusing on the 10-year exposure window, when we restricted the sample to the subgroup with complete exposure information during 10 years preceding hypertension diagnosis, we did not observe meaningful changes in the hypertension risk compared to the main analysis.

In **Paper IV**, we investigated a common threshold for identifying those being at risk of mental illness, instead of population-specific thresholds at the mean of the GHQ-12 summary scale. This analysis resulted in a modest positive association for increasing NDVI in the ESCA study population. We also explored green and blue space exposure in closer proximity to residential addresses, by using natural space exposure data within a 300 m buffer, instead of the 1000 m buffer in the main analysis. The associations were overall similar for the smaller buffer, except for a borderline significant positive association between increasing NDVI and mental health.

4.6 ANALYSES OF COMBINED EXPOSURES

In **Paper II**, we analyzed change in waist circumference in relation to NDVI exposure in combination with air pollution, transportation noise and distance to blue space. In women, NDVI appeared to counteract the effect of both NO_x and transportation noise, when comparing high NDVI and low versus high exposure to NO_x and transportation noise, respectively (Table 7). In men, a similar tendency was observed for transportation noise only. In the subgroups of individuals exposed to low NDVI, high exposure to NO_x and to transportation noise exposure as well as long distance to blue space, we observed a particularly large annual increase in waist circumference in both sexes.

Table 7. Change in waist circumference (cm/year) at combinations of different environmental exposures (beta-coefficients (β) and 95% confidence intervals (95% CI)).

Environmental exposures ^a	Women		Men	
	n	β (95% CI) ^b	n	β (95% CI) ^b
high NDVI and low NO _x	960	(ref)	787	(ref)
high NDVI and high NO _x	430	0.09 (0.00; 0.18)	386	-0.10 (-0.17; -0.02)
low NDVI and low NO _x	498	0.09 (0.00; 0.17)	327	0.02 (-0.06; 0.10)
low NDVI and high NO _x	1052	0.19 (0.12; 0.26)	686	-0.07 (-0.13; -0.01)
high NDVI and low transportation noise	914	(ref)	783	(ref)
high NDVI and high transportation noise	476	0.17 (0.08; 0.26)	390	0.14 (0.06; 0.22)
low NDVI and low transportation noise	585	0.09 (0.01; 0.17)	423	-0.06 (-0.13; 0.02)
low NDVI and high transportation noise	965	0.19 (0.12; 0.27)	590	0.15 (0.08; 0.22)
high NDVI and short distance to blue space	821	(ref)	735	(ref)
high NDVI and long distance to blue space	569	0.02 (-0.07; 0.10)	438	-0.03 (-0.10; 0.05)
low NDVI and short distance to blue space	618	0.08 (-0.00; 0.16)	403	-0.03 (-0.10; 0.05)
low NDVI and long distance to blue space	932	0.17 (0.09; 0.24)	610	-0.02 (-0.09; 0.05)
high NDVI, low noise, low NO _x and short distance to blue space	525	(ref)	435	(ref)
low NDVI, high noise, high NO _x and long distance to blue space	491	0.31 (0.22; 0.40)	268	0.17 (0.08; 0.26)

^a NDVI, NO_x and distance to blue space above vs below the median, any transportation noise (road, railway or aircraft) above vs below 45 dB L_{den}.

^b Models are adjusted for age, alcohol consumption, tobacco use, psychological distress, shift work, aircraft noise, railway noise and distance to blue space.

In **Papers II** and **III**, we investigated potential effect modification by individual, contextual and environmental covariates. In **Paper II**, we observed statistically significant interactions for education level ($p=0.08$), SAMS mean income (lower neighborhood income, *i.e.* contextual SES, $p=0.01$) and tobacco use ($p=0.05$) on change in waist circumference in women (Figure 2). Among individuals with lower education level, and lower SAMS mean income, respectively, we observed a stronger reduction in waist circumference increase associated with one IQR increase in NDVI. We also observed a stronger association among never or former tobacco users, compared to current users. In **Paper III**, we observed statistically significant interactions for road traffic and aircraft noise on hypertension risk (Figure 3). Among individuals exposed to road traffic noise ≥ 53 dB L_{den} ($p=0.004$) and aircraft noise to ≥ 45 dB L_{den} ($p=0.069$), respectively, one IQR increase in NDVI was associated with a more pronounced hypertension risk reduction, compared to individuals exposed to noise levels below these thresholds.

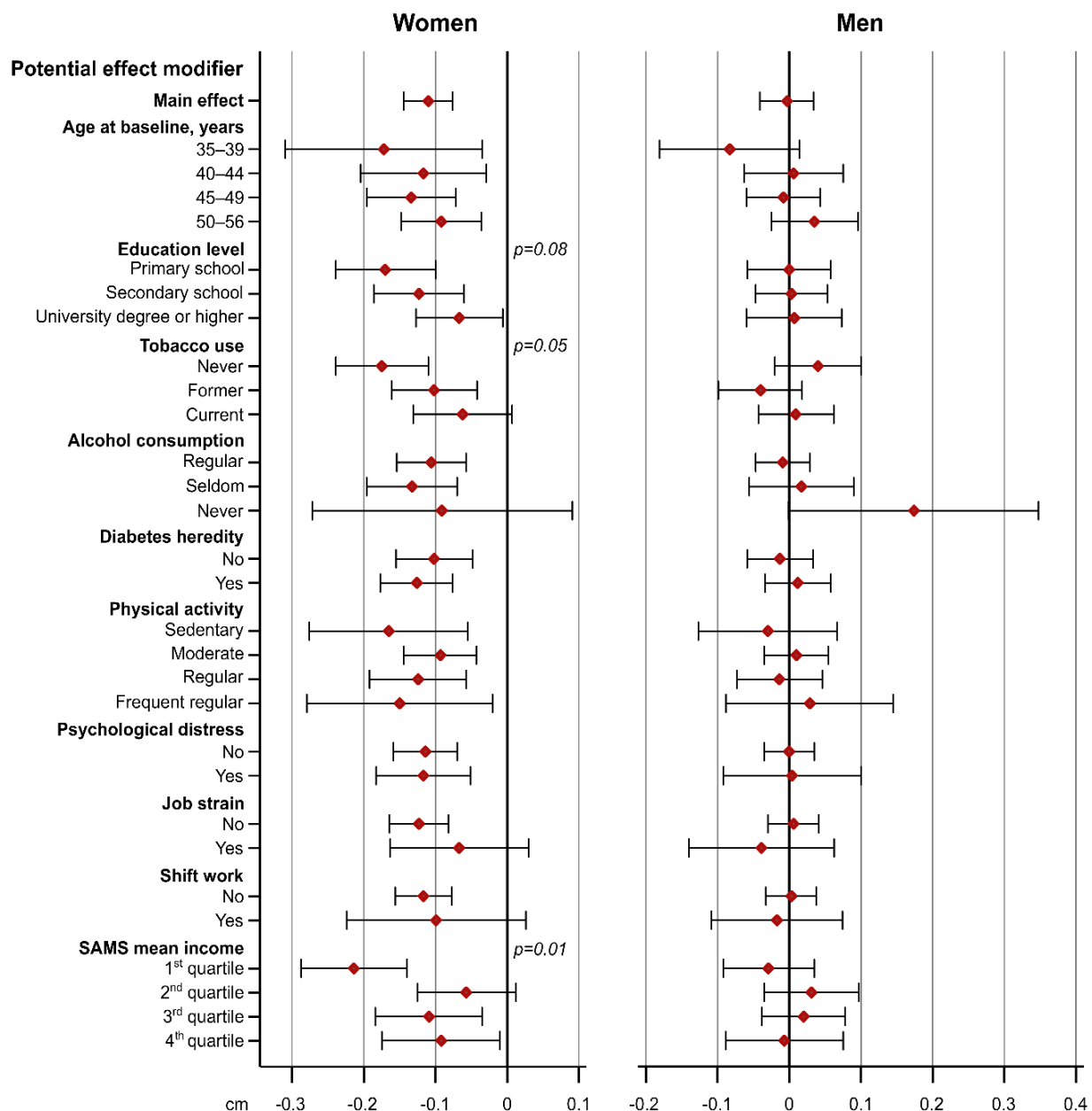


Figure 2. Change in waist circumference associated with one IQR increase in NDVI in 500 m radii buffers, as time-weighted average during follow-up, with potential effect modifiers.

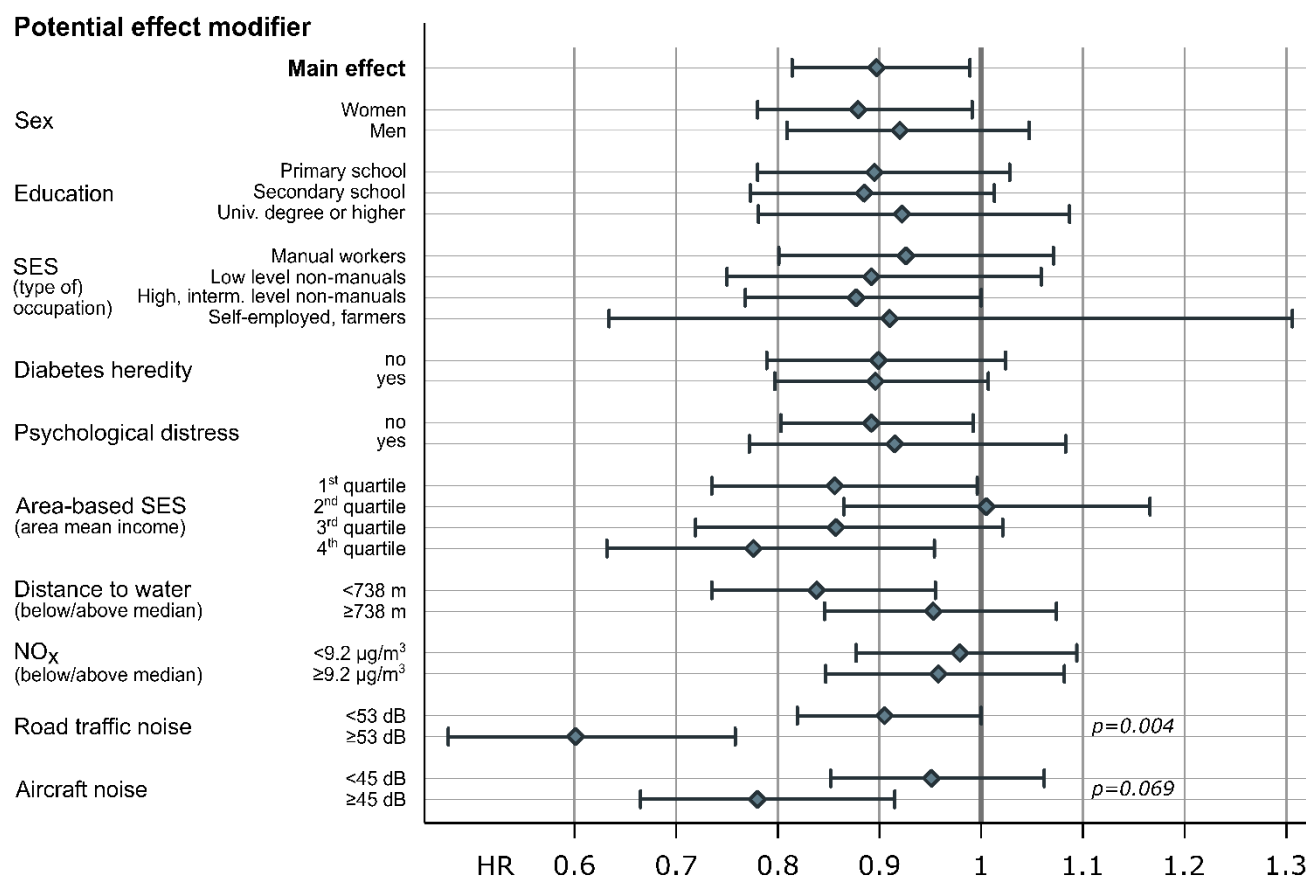


Figure 3. Hazard ratios and 95% confidence intervals for hypertension associated with one IQR increase in NDVI in 500 m radii buffers, as time-weighted average 5 years preceding the hypertension incidence, and interactions between NDVI and the covariates investigated.

5 DISCUSSION

In this doctoral thesis, we aimed to investigate the associations between residential greenness and physical activity, adiposity measures and hypertension, as well as general and mental health. We also aimed to explore factors that may modify the relation between greenness and the outcomes: air pollution, transportation noise and blue space, as well as sociodemographic, behavioral and socioeconomic factors. In the following sections we discuss the findings in the light of previous research. We also discuss methodological considerations, in general in epidemiological studies and in this area of research, as well as the individual studies.

5.1 MAIN FINDINGS

5.1.1 Physical activity

The results of **Paper I** indicated that changes in residential greenness levels as a result of changing address, were related to physical activity levels, but not in the expected direction. Moving to a less green area was associated with increased walking/cycling, and moving to a greener area was associated with decreased walking/cycling. Moving to a less green area and to a greener area were both associated with decreased exercise, compared to staying at the same greenness level.

Reviews which include studies on greenness and physical activity relationship have mostly found positive associations, suggesting that greenness may promote physical activity (Fong et al. 2018; James et al. 2015). Some studies have, however, reported no (Hillsdon et al. 2006; Ord et al. 2013) or inverse associations between greenness and leisure time walking as well as cycling (Maas et al. 2008).

A few studies have found inverse associations between greenness exposure and active transportation levels. Hogendorf et al. (2020) studied changes in physical activity patterns in relation to changes in residential green space exposure among non-movers in Eindhoven, the Netherlands. The authors did not find associations between green space measures and walking and cycling at baseline but found that increased distance to green space was associated with less leisure-time walking but more time walking for active commute. No changes in cycling, and no clear associations for green areas within 1000 m buffers, were observed. Van Heeswijck et al. (2015) found that increased residential NDVI was associated with reduced odds of active transportation (cycling or walking) in Montreal, Canada, after adjustment for individual and contextual demographic and socioeconomic factors, transportation access and commute distance.

These results are in agreement with our findings and may indicate that location-specific connectivity and walkability can be negatively correlated with greenness levels in certain areas. In general, more greenness can be found in suburban and rural areas than in more urbanized areas; however, the area-level connectivity and walkability is likely to decrease outside built-up areas, making the local population more car-dependent in their movements

(Blecic et al. 2017). The physical environment is suggested to influence physical activity patterns through land use and transportation systems, for example high street-connectivity and residential density, as well as the presence of functional sidewalks and bicycle lanes are likely to facilitate and support physical activity (Institute of Medicine and National Research Council 2009; Owen et al. 2014). Thus, it is possible that the macro-level urban form influences opportunities to be physically active, *i.e.* that greener (and less densely built) areas may be located at longer distances from services and facilities. Increased dependence on motorized transport and possible longer commuting time may result in less time available for leisure-time physical activity. It should, however, be noted that, the proportion of movers in our study population was small (10%), which may have reduced the power to detect alterations in physical activity levels in relation to changed greenness.

Physical activity patterns have also been proposed to be related to different individual, interpersonal, environmental, and policy factors, both independently and in interaction with each other (Condello et al. 2017). We did not have information about other possibly greenness-related physical activities, such as gardening and outdoor-time with children. Having a private garden or a children's play area close-by is likely to be location/area-dependent and may affect an individual's wish to either stay put or change their area of residency. Changes in an individuals' life situation may thus trigger moving to a different area, and moving is likely to occur at specific periods in life. Unfortunately, data about these, possible underlying factors were not available.

Among individuals who moved between 2010 and 2014, both moving to a greener and to a less green area was associated with changes in physical activity pattern. There is a possibility that our results reflect the effect of changed life situation rather than the effect of changed surrounding greenness level. Other studies have reported similar findings. For example, a study conducted in Southern Sweden by Weimann et al. (2015) found positive associations between perceived greenness quality and general health in a cross-sectional analysis. However, when the authors analyzed the effect of increased greenness quality as a result of moving on general health, no significant associations were found, except in a subgroup with the lowest prognostic of good general health. The authors concluded that moving or non-moving is most likely not a random phenomenon and that it may occur as a result of factors that the individual cannot control. Furthermore, the findings by Weimann et al. (2015) may imply that individuals who do not have the opportunity to move to greener areas, may be the ones that would benefit the most by doing so, or by increasing greenness exposure in other ways.

5.1.2 Overweight and obesity

In **Paper II**, we found that higher levels of residential greenness during a nine-year follow-up period were associated with a reduced increase in waist circumference in women in 100, 250 and 500 m radii buffers, and reduced risk of central obesity in 500 m radius buffer. We did not observe any association with central obesity measures in men, but we detected an increased risk for overweight with increased NDVI exposure in the 100 m radius buffer.

Moreover, we found that low NDVI exposure in combination with exposure to high levels of NO_x from road traffic, transportation noise, and living far from blue space, appeared to be associated with increased waist circumference in both sexes.

Our result did not agree with many previous reports that have associated BMI-based measures of general overweight and obesity to reduced greenness levels (e.g. Luo et al. 2020; Pereira et al. 2013; Veitch et al. 2016). Few previous studies have investigated other adiposity measures than BMI in relation to greenness. Regarding central obesity, a few previous studies have, similarly to us, found a significant inverse relationship between waist circumference measures and residential greenness levels. For example, a large cross-sectional study, conducted in the UK, found that increased residential NDVI was associated with smaller waist circumference (-0.55 cm, 95% CI: -0.61; -0.50 cm per 1 IQR increase in NDVI) (Sarkar 2017). The author also observed lower BMI (-0.12 kg/m², 95% CI: -0.14; -0.10 kg/m²), and whole-body fat content (-0.14 kg, 95% CI: -0.18; -0.10 kg) to be associated with increased NDVI. Our findings were also partly supported by another recent cross-sectional study from China, which reported that higher residential NDVI values were associated with both BMI (-0.18 kg/m², 95% CI: -0.24; -0.11, per 1 IQR increase in NDVI) and general (OR 0.80, 95% CI 0.74; 0.87) and central obesity (OR 0.88, 95% CI 0.83; 0.93), but not with the continuous measures of the waist circumference (-0.14 cm, 95% CI -0.32; 0.04) (Huang et al. 2020).

Exposure to transportation noise (including road, railway and aircraft noise) and air pollution have been associated with both cardiovascular and metabolic disease risk (Bourdrel et al. 2017; Cesaroni et al. 2014; Kempen et al. 2018; Munzel et al. 2017). Greenness has been suggested to mitigate harmful effects of these exposures (WHO 2016a). A few studies have investigated if exposure to blue space is associated with either BMI or central obesity measurements. Some of these report significant findings (Qin et al. 2012; Witten et al. 2008; Wood et al. 2016; Zhang et al. 2014), while others do not (Halonen et al. 2014; Modesti et al. 2013; Turek et al. 2001; Ying et al. 2015). From our results, it appears that exposure to increased levels of air pollution and noise as well as increased distance to blue space, are associated with changes in waist circumference both at high and low NDVI exposure values in women, but this only held true for noise in men. In both sexes a particularly strong increase in waist circumference was indicated in those exposed to low NDVI, high exposure to NO_x and to transportation noise exposure as well as long distance to blue space. This may suggest that a combination of adverse environmental exposures is particularly harmful.

5.1.3 Hypertension

In **Paper III**, residential greenness exposure five years prior to diagnosis was found to be associated with reduced hypertension risk. No relation between greenness and hypertension risk was found for the ten-year exposure period prior to diagnosis. Among individuals exposed to higher residential levels of road traffic noise (≥ 53 dB L_{den}) and aircraft noise (≥ 45 dB L_{den}), we found a more pronounced inverse association between greenness exposure and hypertension incidence.

Evidence for an association between hypertension risk and greenness exposure from previous studies appears inconclusive, with systematic reviews reporting an overall mixed picture (de Keijzer et al. 2020; Fong et al. 2018). Cross-sectional studies including Dutch and German adolescents, respectively, have either not observed clear associations between greenness and high blood pressure or hypertension, or have reported inconsistent patterns (Bloemsma et al. 2019; Jendrossek et al. 2017). Among the few longitudinal studies that have been published, one study from Australia found that hypertension risk appeared to decrease with increased tree canopy cover, but not with the total neighborhood green space, whereas another Australian study did not find associations between greenness in public open spaces and hypertension risk (Paquet et al. 2014).

The observed absence of a statistically significant association between greenness and hypertension risk when a ten-year exposure period prior to diagnosis was used may have several explanations. For example, a longer follow-up period may have given rise to a larger bias due to non-differential misclassification of the NDVI exposure at residential locations with uncertain exposure information before baseline examinations. However, our sensitivity analysis with the sample restricted to individuals with complete exposure information only, did not change the non-significant association. Another explanation could be that the greenness exposure closer in time to the diagnosis was more etiologically relevant. According to several experimental studies, the effect of greenness on blood pressure is rather acute (Park et al. 2010). Thus, associations between greenness and blood pressure may be easier to detect after a shorter exposure period. However, it is not clear if the findings from experimental and observational studies can be related to longer-term cardiovascular disease risk, including hypertension (Hartig et al. 2014; Kondo et al. 2018; Markevych et al. 2017).

In our study, a sensitivity analysis indicated that the inverse association between greenness and hypertension was statistically significant only for the hypertension cases identified from blood pressure measurements at the follow-up clinical examinations. No statistically significant association was observed for the hypertension cases identified through questionnaires or from the national patient register. This may be related to differences between the two subgroups concerning such as socio-economic status, health-related behavior and awareness, and/or comorbidities. For example, among chronically ill patients who may have sought medical care, hypertension might have been detected earlier compared to individuals who were generally healthier or less health aware. This effect on the time point of hypertension case detection may have reduced the ability to detect incidence of hypertension in relation to long-term greenness exposure. Another explanation may be that identifying hypertension cases with blood pressure measurements may have a higher validity than self-reported questionnaire information on previous hypertension diagnosis or treatment (potentially affected by recall bias). Finally, subgroup results in the sensitivity analyses need to be interpreted with some caution due to the increased risk of chance findings.

5.1.4 General and mental health

In **Paper IV**, we analyzed associations between greenness and blue space, and general and mental health in three European data sets and conducted meta-analysis to generate pooled estimates. Our results indicated a few statistically significant associations in the individual surveys, but without any consistent patterns. The results from the meta-analysis did not provide evidence of associations between residential green and blue environments, and general or mental health.

A large body of research point towards positive associations between natural environments and general as well as mental health (Bratman et al. 2019; Gascon et al. 2017; Hartig et al. 2014; White et al. 2017). However, the considerable heterogeneity in study designs, exposure definitions and assessment, outcome assessment, confounding control and operationalization and reporting, make between-study comparisons and aggregation of results difficult (Wendelboe-Nelson et al. 2019).

The inconsistent distribution of significant findings among subgroup studies and no major significant trends in the meta-analysis complicates the interpretation of our results. We found that 5-10% green space in 1000 m buffer was associated with lower odds of good general health, *i.e.* poorer general health, compared to having 0-5% green space. We also observed that an increasing distance to the nearest river was associated with higher odds of good general health both in the Swedish study population and in the meta-analysis. These unexpected associations were likely to be caused by residual confounding. It is possible that we, for example, were not able to account for some important demographic or socioeconomic factors, which confounded the associations.

We did not observe any significant associations between the exposure to various blue and green environments and mental health in the meta-analysis, however, several country-level analyses resulted in significant findings indicating positive associations between nature exposure and mental health. The lack of clear overall patterns in the meta-analysis may indicate that nature-health associations are relative, rather than being absolute, and that using harmonized data across different geographical areas results in biased estimates. The links between exposure to natural environments and human health effects may not be universal and cannot therefore be analyzed using the same exposure assessment methods, categorizations and analytical approaches.

A further reason to the lack of significant pooled estimates may be related to limited possibility to account for air pollution and noise exposure. Both these exposures have been linked to a range of health outcomes but tend to be negatively correlated with greenness exposure. Not adjusting for them may affect the possibility to detect associations the effect of one particular exposure if others are not adjusted for. Klompmaker et al. (2019) suggests that only adjusting for one of these exposures (greenness, air pollution, or road traffic noise) may either over- or underestimate the association with health outcomes attributed to that exposure.

Consequently, the lack of air pollution and noise data may have contributed to the inconsistencies of our findings.

5.1.5 Effect modification

In **Paper II**, we observed effect modification by sex, and in women by SES; area-based mean income, and a tendency of modification by individual education. Stronger associations between increased greenness and reduced increase in waist circumference were observed at lower levels of area-based mean income and education. As far as we are aware, no previous longitudinal studies that have used central obesity as an adiposity indicator have observed effect modification by sex in the greenness-adiposity relationship. However, a few cross-sectional studies have observed that proximity to green space appeared to be associated with decreased risk of general overweight and obesity in women, but not in men (Astell-Burt et al. 2014; Wen et al. 2011). Prince et al. (2011) observed increased odds of overweight and obesity in men, and decreased odds of overweight/obesity in women, in relation to more green space. Possible explanations to sex differences may be related to differences in perceptions and behavior in relation to greenness. The fact that adipose tissue function and deposition differ between the sexes could also contribute, and may be differently related to environmental and behavioral factors, and in relation to changes over a life course, which may affect our possibility to detect possible associations with greenness. With age, men tend to acquire more visceral fat, whereas a shift in adipose deposition occurs during menopause in women, from hips and thighs, to the abdomen. With men generally more prone to acquire visceral fat compared to women, potential effects of greenness exposure on waist circumference may be more easily detectable in females than in males.

In **Paper II**, the observed effect modification by SES confirms findings from previous studies on adiposity measures (Sarkar 2017) and other health outcomes (Groenewegen et al. 2018; Mitchell and Popham 2008) which have found that to lower SES groups appear to benefit more from higher levels of residential greenness. The reasons may be related to limited resources, affecting mobility, and results in higher dependency on the near environment. This may lead to stronger associations with residential environmental factors, compared to higher SES groups, whose greenness exposure may also occur at locations further away from the residential address, such as second homes. This may result in a higher degree of exposure misclassification and a risk of a dilution of the estimates.

In **Paper III**, we observed a more pronounced hypertension risk reduction from increased five-year greenness exposure among individuals exposed to higher residential levels of road traffic noise (≥ 53 dB L_{den}) or aircraft noise (≥ 45 dB L_{den}). This is in line with previous studies suggesting a potential buffering effect of greenness exposure against harmful environmental exposures (Ow and Ghosh 2017; Yang et al. 2011). Our results could be explained either by physical shielding or increased absorption or by reduced noise-induced stress response. This may imply that individuals exposed to high noise exposures might benefit more from increased greenness exposure, compared to individuals exposed to lower noise levels.

5.1.6 Pathways involved in the greenness-health relationship

The suggested pathways linking greenness exposure to health were outlined in section 1.3. In this thesis, we have explored the relationships between greenness and physical activity, adiposity, hypertension, and general and mental health. We have discussed possible pathways involved in the outcomes of interest. In **Paper I**, we found that change in greenness exposure following moving and change in physical activity were associated, but not in the expected direction. Greenness, measured by NDVI, may be related to the macro-level urban structure which sets the “baseline” preconditions for the opportunity to be physically active. To further explore physical environment determinants of physical activity, including interactions between green environments and other aspects of the physical environment, advancing methodologies involving detailed street-level information on possible health-promoting factors to develop concepts such as walkability, may provide more insight into the connections between the built and green environment, physical activity and health (James et al. 2017; Paquet et al. 2014; Sarkar et al. 2018). In conclusion, based on our results, we cannot draw conclusions about associations between residential greenness and physical activity. However, we may conclude that moving to an area with lower or higher greenness level appears to be associated with changes in physical activity. Further investigations of the role of the physical environment and structure at street-level as well as city-level in relation to health-related behavior, together with investigations of determinants of moving or not moving in relation to environmental exposures, are warranted.

In **Paper II**, we found that greenness exposure was associated with reduced increase in waist circumference and incidence of central obesity in women. These results may be related to the possible pathways via greenness’ stress-reducing and restorative properties via the Hypothalamic-Pituitary-Adrenal (HPA) axis, which may affect long-term development of overweight and obesity, in particular central obesity (Dhabhar 2014). According to the Psycho-Physiological Stress Reduction Theory, greenness exposure may buffer physiological stress responses involving activation of the sympathetic nervous system and the HPA axis (Berto 2014; Ulrich et al. 1983). Acute stress responses involve a cascade of physiological reactions: release of cortisol, immune system suppression, increased blood pressure, heart rate, blood sugars and fats, increased blood flow to the muscles, aggregation of thrombocytes, in order to mobilize energy and strength, and protect the body from injuries and prevent blood loss, *i.e.* prepare the body for “fight-or-flight”. Long-term activation of these systems can lead to elevated blood pressure, atherosclerosis and metabolic dysregulation, leading to insulin resistance and weight gain, which may contribute to the development of cardiovascular and metabolic diseases (Kivimaki and Steptoe 2018). It has been suggested that greenness exposure can stimulate downregulation of the stress responses, and support relaxation and restoration, and thereby preventing harmful effects from long-term stress exposure (WHO 2016a).

Moreover, biological and/or behavioral differences between women and men may explain the sex differences in associations. In **Paper III**, greenness exposure 5 years prior to diagnosis was associated with incidence of hypertension. Risk factors for the development of

hypertension include environmental and behavioral factors, among them chronic stress (Sparrenberger et al. 2008). However, in our statistical models, only psychological distress was observed to be significantly associated with hypertension risk among the covariates reflecting different types of stress (job strain, shift work and psychological distress), and sensitivity analysis, excluding psychological stress, did not change the estimate. **Papers II and III** also investigated and discussed potential mitigation of the negative health effects of the environmental exposures noise, air pollution and lack of blue space. In conclusion, based on our results, we can neither confirm nor discard this link between greenness and health.

Paper IV provided limited insight in the possible pathways involved in the greenness-health relationship. The cross-sectional study design prevents from conclusions about causal relationships.

To conclude, the health outcomes studied in this thesis are mainly results of long-term exposures to behavioral and environmental (and genetic) factors. A considerable number of studies have observed inverse associations with short-term stress-related biomarkers (Bratman et al. 2015; Park et al. 2010; Ward Thompson et al. 2012; WHO 2016a). However, there are uncertainties in how these measurable, acute effects translate into long-term, significant health effects, such as reduced cardiovascular and metabolic disease risk (Rook 2013). Further research into the less explored links, such as the role of the immune system and possible interactions with psychophysiological factors, may contribute to more knowledge about the pathway linking greenness to health.

5.2 METHODOLOGICAL CONSIDERATIONS

Papers I and IV are based on population-based surveys, which, in brief, were initiated to study distribution of health outcomes, health-related behavior and other risk factors in the population (Fridh et al. 2013; Generalitat De Catalunya Departament De Salut 2012; Svensson et al. 2013; University of Essex and Institute for Social and Economic Research 2019). The fact that they were not designed to primarily study the outcomes in relation to the exposures of interest in our papers, may have affected the validity of the results.

The study populations in **Papers I and IV** are based on random samples of the general population of each geographical area. The SPHC study population in **Paper I** was using stratification by residential municipality. The PHS, UKHLS and ESCA study populations used in **Paper IV** used a sampling design involving stratification, clustering and weighting as a way of accounting for underrepresentation of certain groups and geographical areas. These measures aimed at increasing the representativeness of the samples. However, with response rates at 67% in the SPHC and 80% in SDPP, there is a risk of selection bias due to potential selective study participation. Individuals who chose to participate in the study may *e.g.* have higher education and be more interested and aware of their health, compared to the general population. They may have higher income and can afford to live in green areas, and they may also be more inclined to be physically active, *i.e.* factors related directly or indirectly to the

main exposures and outcomes of interest. As a result, the associations may appear stronger in the study population, compared to factual associations in the general population.

Another potential risk of bias is self-selection into residential areas with more health-promoting factors, which has been proposed by Katz (2009). Associations may be confounded due to self-selection, *i.e.* that people who are more motivated to be physically active, spend time in green areas, eat well and can afford to live in areas that support this lifestyle. Adjusting for preferences for certain environments is difficult, but we believe that adjusting for different measures of socio-economic status account for SES-driven health-related behaviors and thus reduce the risk of confounding.

In **Paper I**, a concern is the analytical approach of studying changes in greenness levels as a result of changing address. We did not have information about the underlying factors that may have determined the change in residency, factors that may have influenced the changes in physical activity and thus confounded the association. However, by adjusting for potential confounders, as well as conducting stratified analyses, we believe that the risk of residual confounding was reduced. In **Paper IV**, the harmonization of exposure variables and covariates across the study populations, by using the same categorizations in all three populations, may have resulted in categories not adequately reflecting associated risks and meanings of covariates in relation to exposures within each population. This might have resulted in misclassification and a risk of dilution of the associations. For example, the presence of green and blue space may be differently related to socio-economic or behavioral factors in each geographical area. In addition, the harmonization across the three surveys, in terms of adjustment for the same set of covariates, restricted us from accounting for potential confounders, such as physical activity, alcohol consumption and smoking habits. In addition, the possible associations between green/blue space and general and mental health may be relative in, and specific to, each geographical area. For example, the benefits of an increase in greenness may be larger at generally low levels of greenness, compared to areas where there is more greenness.

Papers II and III are based on a cohort established with the overall objective to study risk factors and prevention methods for type 2 diabetes by recruiting a study population where approximately 50% of the participants had diabetes heredity (Stjernschantz Forsberg et al. 2016). Thus, the cohort was not primarily established to study changes in adiposity markers and incidence of hypertension in relation to greenness exposure. This may have affected the generalizability of our findings, if risk factors were differently distributed in the study population, compared to the general population. In **Paper II**, we accounted for diabetes heredity by conducting sensitivity analysis with a sample restricted to those without diabetes heredity but did not observe any meaningful changes in the association. In **Paper III**, we adjusted for diabetes heredity in all analysis in order to reduce the potential risk of bias due to diabetes heredity.

Estimating the exposure to greenness has several challenges. NDVI is an indicator of the amount of vegetation, rather than the type of vegetation, facilities or what type of activities

can take place there. Neither do we have information about accessibility, perceived safety, management and maintenance of the green space and other factors that may promote or restrict individuals from using the green areas. Moreover, estimating NDVI exposure at residential addresses is only a proxy for the total greenness exposure. We did not have information about the NDVI level in other locations where the participants spent time, such as work, commuting, and leisure time locations. The uncertainty surrounding the actual exposure to greenness may have resulted in exposure misclassification. However, we believe that most people do spend time in and near their homes, and that estimated residential greenness exposure is a good proxy for total exposure. In addition, in **Papers II** and **III**, we used a detailed spatial (30*30 m) and temporal (yearly) greenness exposure assessment, estimated at each address, and we calculated the time-weighted average exposure during the entire follow-up period. In **Paper I**, neighborhood greenness at baseline as well as follow-up was estimated. All together, we believe that these measures reduced the risk of potential exposure misclassification. Although the less detailed resolution of the NDVI data in **Paper IV**, 250*250 m, may have resulted in some misclassification and some possible dilution of estimates, it is unlikely that potential exposure misclassification would be differential with regard to the outcomes. To improve the exposure assessment, methodologies involving individual tracking and measurement by using Global Positioning Systems (GPS) and accelerometry, as well as collecting information on perceptions and preferences towards greenness in investigating greenness effects on health-related behavior and outcomes, may provide higher precision and accuracy (Yi et al. 2019).

A wide range of greenness indicators exist, and each one may capture different aspects of greenness, and may be related to different pathways through which greenness may be linked to health. For example, physical activity may be more closely related to accessible green areas of a particular minimum size, whereas mitigation of the effect of pollutants may be more related to availability and location of the greenness in relation to the sources of pollutants. Future studies may benefit from exploring further how different greenness indicators relate to different outcomes and hypothesized pathways in order to gain more insight into the mechanisms involved in the greenness-health relationship.

Several studies have investigated concomitant exposure to different environmental factors in order to assess independent as well as combined effects of spatially correlated exposures on health outcomes. This is of importance for translating research into practice and providing guidance in the potential trade-offs involved in various land-use, transportation and infrastructure decisions, as well as in public health policies. However, a review evaluating studies of combined effects of spatially correlated exposures, found that few studies were able to assess such effects due to a lack of standards in measurement and high risk of bias (Rugel and Brauer 2020). The authors concluded that when the complexity of the exposure-health relationships is properly accounted for, there still appears to be distinct effects of the spatially correlated exposures. Considering greenness, a few of the studies found indications of partial mitigation by exposure to natural spaces on adverse effects of air pollution and/or noise (Rugel and Brauer 2020). In our **Papers II–IV**, in addition to greenness exposure

assessment, we also considered other environmental exposures. In **Paper II**, we adjusted for individual, time-weighted average of aircraft noise, railway noise and distance to blue space, and we also examined co-exposures to greenness and air pollution, transportation noise and distance to blue space. In **Paper III**, we adjusted for individual, time-weighted average of NO_x, road traffic and aircraft noise as well as distance to blue space, and further explored potential effect modification by the same set of exposures. In **Paper IV**, the fully adjusted model in all analyses included proportion road area estimated in individual exposure buffers as a proxy of air and noise exposure and potentially other stressors or pollutants. We believe, that adjusting for these exposures reduced the risk of confounding in our studies. For example, in **Paper III** the inverse association between greenness exposure and hypertension risk only became apparent after adjustment for environmental confounders. Future studies should simultaneously assess several environmental exposures, in order to disentangle the role of greenness in relation to other spatially correlated exposures in urban environments.

All four papers included adjustment for a number of individual and contextual covariates in regression models, as well as stratified analysis, to address potential confounding. Detailed covariate information was obtained from questionnaires, registries and clinical examinations. However, we were not able to include data on physical activity, alcohol consumption and smoking habits in **Paper IV** because they were not included in the relevant wave of UKHLS, and therefore also excluded from the analysis of the PHS and ESCA data. Failure to adjust for these factors may have confounded the associations and contributed to the inconsistent results. However, although in all papers included different ways to address confounding, we cannot rule out the risk of residual confounding.

6 CONCLUSIONS

This thesis investigated the relationship between individual exposure to residential greenness and physical activity, adiposity measures and hypertension, as well as general and mental health. Three of the individual studies were based on two cohorts from Stockholm County, Sweden. The fourth study consisted of a meta-analysis based on three cross-sectional studies conducted in Scania, Sweden, England and Wales, the UK, and Catalonia, Spain.

Changing residential greenness exposure as a result of moving appears to affect walking/cycling, and changing to both more and less greenness was related to decreased exercise. The opportunity and motivation for physical activity may be more strongly influenced by macro-level urban form and infrastructural factors such as walkability and distance to services, than by residential greenness availability and accessibility. Individual-level life situation and events most likely also affect physical activity patterns.

We found that long-term greenness exposure was related to a lower risk of central obesity in women, particularly in those with low socioeconomic status. Furthermore, there were increases in waist circumference in both sexes among those exposed to low greenness levels together with high NO_x from road traffic and transportation noise as well as long distance to

blue space. This suggests that a combination of several adverse environmental exposures may be particularly harmful.

Greenness exposure during five years was related to a reduced hypertension risk, whereas exposure during ten years prior to diagnosis was not. Greenness exposure appeared to have a particularly strong protective effect among those exposed to high levels of road traffic or aircraft noise. This emphasizes the potential importance of interactions between environmental exposures and of simultaneously assessing several exposure factors in studies on greenness and health.

Pooled estimates of standardized green and blue space exposures across three European regions did not appear to be associated with self-rated general or mental health. The relationships between natural environments and health outcomes may be specific to each geographical area and the effect of nature may be relative rather than universal.

To summarize, we did not observe clear and consistent associations between greenness and health outcomes. Associations were often observed for subgroups and for specific exposure windows. A suggested mechanistic link between greenness and health in urban areas, is the potential ability of greenness to mitigate the effect of harmful environmental exposures, such as air pollution and transportation noise. Our findings support such mitigating effects by urban greenness on adverse health effects related to air pollution and noise exposure and also point to the importance of adjusting for environmental co-exposures in the analyses. In conclusion, greenness provides a wide range of benefits to urban areas, and may promote health in several, interconnected ways, particularly in vulnerable groups. Further studies using longitudinal study design, exploring less studied pathways, assessing personal greenness exposure, and examining interactions with environmental co-exposures, would advance the research area and elucidate the mechanisms involved in the greenness-health relationship.

7 SVENSK SAMMANFATTNING

Exponering för grönska har visats ha samband med ett brett spektrum av hälsoutfall, bland annat flera sjukdomar som utgör en betydande del av den globala sjukdomsburden, nämligen hjärt-kärlsjukdomar, metabola sjukdomar och psykisk ohälsa. I dag bor över hälften av världens befolkning i städer och påverkas av hälsorisker såsom buller, luftföroreningar och värmeöar, och har begränsad möjlighet till bl.a. fysisk aktivitet och tillgång till hälsosam kost, samt till grönska. Det övergripande syftet med denna avhandling var att undersöka samband mellan grönska vid bostaden och hälsoutfallen fysisk aktivitet, övervikt, fetma och bukfetma, högt blodtryck samt allmän och psykisk hälsa. Dessutom undersöktes om sambanden påverkades av individuella, kontextuella och miljömässiga faktorer, däribland luftföroreningar, transportrelaterat buller och blå miljöer – vatten.

Av avhandlingens fyra delarbeten baserades det första på data från Stockholms folkhälsokohort (42 611 studiedeltagare) från 2010 och 2014. Det andra och det tredje delarbetet baserades på data från Stockholms diabetespreventiva program (5 126 respektive 4 623 studiedeltagare) från 1992–2006. Det fjärde delarbetet var en metaanalys som inkluderade tre tvärsnittundersökningar från södra Sverige, Storbritannien och Spanien (50 220 studiedeltagare) genomförda 2012–2014. Exponering för grönska uppskattades med hjälp av det satellitgenererade indexet Normalized Difference Vegetation Index (NDVI) samt från markanvändningsdata. Utfallsdata baserades på självrapporterad information från enkäter och kliniska undersökningar som kompletterades med registerdata.

Resultaten visade att ökad grönskeexponering i grannskapet till följd av flytt var associerad med minskad gång/cykling. Både ökad och minskad grönskeexponering var förknippad med minskad träning. Exponering för grönska var associerad med mindre ökning av midjemåttet och minskad risk för bukfetma hos kvinnor, men inte hos män. Högre grönskeexponering under en femårsperiod före diagnos var associerad med minskad risk för högt blodtryck. Exponering för högre nivåer av vägtrafikbuller respektive flygtrafikbuller var förknippade med en mer uttalad riskminskning för högt blodtryck vid ökad grönskeexponering, jämfört med vid exponering för lägre bullernivåer. Vi fann inga tydliga mönster i sambanden mellan gröna respektive blå miljöer och allmän eller psykisk hälsa i en metaanalys av tre europeiska tvärsnittundersökningar, och inga tydliga resultat i de enskilda undersökningarna.

Sammanfattningsvis visar våra resultat svaga samband mellan grönska och hälsoutfall, och de observerade sambanden var begränsade till undergrupper och specifika exponeringsfönster. Våra resultat tyder på att sambanden mellan grönska och övervikt/fetma respektive högt blodtryck kan påverkas av samtida exponering för trafikrelaterat buller och luftföroreningar.

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